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CORONARY EMBOLISM*

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MANY years ago, when I came to New York to begin my interneship in medicine at the New York Hospital, Dr. Conner was in charge of the medical service at the Hudson Street Annex. He came often to the old hospital on Fifteenth Street to see interesting cases, and on occasions substituted at ward rounds for the regular attending physician. He was pointed out to me by my associates as the most promising of the young men in New York devoting themselves to internal medicine. It was not difficult for me to accept this high estimate of his character and ability. His comely figure, his courteous and gracious, yet dignified and reserved, manner, his professional ability and untiring zeal set him apart as unusually gifted and determined to make the most of his gifts. Too often does the flame of promise, burning brightly in youth, subside after a few years to a flickering glow that is soon extinguished. Happily, not so in Doctor Conner. With the passing years the early presage of a distinguished career has been increasingly fulfilled, so that now, in the autumn of his life, he has grown to the stature of a great and inspiring physician. The gods seem to have showered upon him all their gifts. Not only has he preserved the figure and physical energy of of youth but as well its mental vigor and indefatigable interest. I have never had the good fortune to be intimately associated with Doctor Conner, but I have seen him often during the intervening years and my admiration and affection steadily have grown.

This being my regard for him you will readily understand what great pleasure I derived from your invitation and that I esteem it a high honor to have been asked to give this lecture.

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When we speak of coronary occlusion we have in mind chiefly coronary thrombosis. Indeed in conversation, and sometimes in medical writings, the terms are used as though they were synonymous. As a matter of fact there is some excuse for this identification since, whatever may be

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the cause of the occlusion, in the end thrombosis nearly always occurs, and thrombosis developing as an independent and primary condition, in the absence of any disease of the arterial wall or its lumen, due solely to some disorder of the blood, is a great rarity. However, as a rule the term thrombosis is not used in this all-inclusive sense, nor is it so understood, but in the more restricted sense of accompanying or following arteriosclerotic disease of the coronary arteries. For instance, were a physician to speak simply of coronary thrombosis I think we would be surprised to learn that he had meant to include under this heading the compression of an artery from without, or inflammation of the wall of an artery as occurs in periarteritis nodosa, or thrombosis following rupture of the artery, or embolic occlusion of an artery, or the gradual sealing of the mouth of a coronary artery by the encroachment of syphilitic disease of the aorta. It is an established custom that when we speak of these uncommon causes of coronary occlusion we are to mention them specifically.

The symptoms and the pathologic anatomy of coronary occlusion have been diligently investigated during the past fifteen years so that at present everyone is familiar with the important clinical facts and their underlying causes. Nevertheless I have no doubt that information of value is still to be got from a detailed study of some of the less common features of the condition. The predominant cause of coronary occlusion is arteriosclerosis, and it predominates to such a degree that we are apt to neglect or forget other occasional causes. I have selected coronary embolism as the topic of my remarks not to excite your curiosity with the details of an idle search for the recondite, but because I believe there is something to be said about it of a little practical importance.

When we consider coronary embolism with our attention focused upon its clinical manifestations, it is desirable to separate the subject into two divisions, embolic occlusion of large coronary branches which are usually single, and embolic occlusion of small coronary branches which are nearly always multiple. This division is desirable because the symptoms of the two conditions are entirely different; therefore, it would be confusing to consider them together. When clinicians speak of coronary embolism, they always have in mind the occlusion of large vessels. Indeed the embolic occlusion of many small branches of the coronary arteries, although it is a condition well known to the pathologist, has not been deemed of sufficient clinical importance to merit more than passing notice.

I. EMBOLIC OCCLUSION OF LARGE BRANCHES OF THE CORONARY ARTERIES

Saphir, in 1932, collected from the literature sixteen cases of coronary embolism and added to these three cases he had observed himself. Without pretending to have made a thorough search I have found eleven cases reported since the publication of Saphir's article. In the index of the

pathologic records of the Johns Hopkins Hospital the diagnosis of coronary embolism appears for the first time in 1931. During the nine succeeding years, from 1931 to 1939, the diagnosis has been entered ten times. An analysis of these forty cases will furnish the substance of my remarks.

I would not have you believe that only forty instances of coronary embolism have occurred since the first observation briefly reported by Virchow in 1856. The condition would be very rare indeed were this inference tenable. On the contrary there are many valid reasons for concluding that coronary embolism is much more frequent than these figures indicate. It is only reasonable to assume that but a small number of the cases encountered at autopsy have been reported. As I shall have occasion to point out later, the most frequent source of coronary emboli is bacterial vegetations upon the heart valves. This association is so frequently observed as to be almost a commonplace, and it would be trite to report these cases unless the circumstances of a particular instance were unusual or else as part of a statistical study. At present we can form no accurate estimate of the true incidence of coronary embolism although the results of a number of statistical studies allow an approximation. For instance Levy, Bruenn, and Kurtz found six instances of embolism in a study of the pathologic records of 762 cases of coronary occlusion; Appelbaum and Nicolson four cases of embolism, all due to bacterial vegetations, among 168 cases; Kirschbaum four instances of embolism, all associated with bacterial endocarditis, among 612 cases of severe disease of the coronary arteries. Moreover it is likely that many instances of embolism have been misinterpreted at the post-mortem examination. As a rule it is difficult to establish the diagnosis of coronary embolism, and only rarely would the diagnosis be made unless the possibility of its occurrence were kept in mind and the evidence carefully sought for. The fact that the diagnosis of coronary embolism was registered for the first time at the Johns Hopkins Hospital in 1931 and ten times in the succeeding nine years invites comment. Shall we conclude that the condition had not occurred during the more than fifty years before 1931 and then suddenly had occurred ten times during the following nine years? This is improbable to the last degree. It is certainly true that we see what we look for, and this adage no doubt explains the sudden occurrence and the sustained incidence of coronary embolism. I think we may conservatively estimate that from 1 to 2 per cent of the cases of coronary occlusion are due to embolism, and I predict that the proportion will rise as interest and familiarity incite more thorough investigation.

There are six possible sources for emboli which may occlude the coronary arteries: (1) A thrombus or atheromatous material in a coronary artery; (2) a thrombus covering an arteriosclerotic plaque at the root of the aorta; (3) bacterial vegetations upon the mitral or aortic valves; (4) intracardiac mural thrombi; (5) thrombi in the pulmonary veins; (6)

thrombi in the peripheral veins, parodoxical embolism. Instances of coronary embolism from all six of these sources have been reported. In the forty collected cases the source of the embolus is not stated in two. In the remaining thirty-eight cases two belong in the first group, six in the second, nineteen in the third, five in the fourth, two in the fifth, and four in the sixth.

1. *Emboli coming from a thrombus or atheromatous material in a coronary artery*

This form of coronary embolism has little clinical interest. Since it follows disease of the coronary arteries in most instances it will add nothing to the symptoms already present, or at most unimportant details. Occasionally calcareous deposits on an atheromatous ulcer in a large coronary artery may become detached without a thrombus being formed at that location, and these free deposits, propelled by the blood stream, may lodge at the first point of bifurcation they meet, producing occlusion at this point. Or, a thrombus on a sclerotic patch which does not completely obstruct the lumen may become loosened and occlude a smaller branch further on. Under these circumstances literally the coronary occlusion is the result of embolism but the embolus is incidental to already existing coronary disease. This is a different matter from an embolus entering the coronary circulation from without. Whatever interest may be attached to it concerns the pathologist more than it does the clinician. Nevertheless for the sake of completeness I will notice briefly the two cases which have been reported.

Huber, in 1882, reported the case of a man of 64 years who had died suddenly. At autopsy an embolus was found occluding the descending branch of the left coronary artery. The embolus had come from a thrombus in the main stem of the left coronary artery.

Saphir describes the heart of a man of 70 years who entered the hospital with typical attacks of angina pectoris. The heart was enlarged, the sounds feeble, and a pericardial friction was heard. There were the usual signs of a moderate degree of chronic passive congestion. A few days after admission auricular fibrillation came on. Under treatment the patient improved somewhat but on the sixth hospital day he died suddenly. The post-mortem examination disclosed diffuse arteriosclerosis and advanced sclerosis of the coronary arteries. The heart was hypertrophied and dilated. There was recent infarction of the lateroposterior wall of the left ventricle. There was an acute fibrinous pericarditis. In the circumflex branch of the right coronary artery, at a point about 1 cm. from its mouth, there was an atheromatous ulcer with a small thrombus over it; at the point where the posterior descending branch comes off from the circumflex artery, there was an embolus about 1 cm. in length which completely occluded the lumen of the right branch of the circumflex artery.

2. *Coronary emboli coming from thrombi located upon arteriosclerotic plaques at the root of the aorta*

I was surprised to find six instances of this condition among the thirty-eight collected cases. In point of incidence it is second only to bacterial endocarditis.

The first case was reported by Hektoen in 1892. A man, 32 years of age, died suddenly. An embolus was found in the left coronary artery at the site of division into the descending and circumflex branches. The embolus had come from a parietal thrombus in the aorta.

Oestreich reports the case of a man, 30 years of age, who died suddenly on the night of his wedding. There was an arteriosclerotic ulcer covered by a thrombus at the root of the aorta. The mural thrombus had occluded the mouth of the right coronary artery. There was an embolus in the main stem of the left coronary artery.

Chiari performed the autopsy upon a man of 32 who had died suddenly. There was embolic occlusion of the main stem of the left coronary artery and an organizing thrombus occluding the mouth of the right coronary. The source of the embolus was a thrombus covering a small atheromatous ulcer in the aorta.

Kauffman's case was that of a man, 35 years of age, who had died suddenly. An embolus was found in the descending branch of the left coronary artery which had come from a thrombus on the aortic wall just above the posterior cusp of the aortic valve.

The patient reported by Saphir was a man, 72 years of age, who had had attacks of angina pectoris for 17 years. A little over a year before he died he had had an attack diagnosed coronary thrombosis. He recovered and was well for a year, when he had a second severe attack, followed by the symptoms of myocardial insufficiency. Under treatment he improved but died suddenly three weeks after the onset of the attack. The heart was enlarged. At the left apex there was an aneurysm. The myocardium was diffusely fibrotic. There was pronounced sclerosis of the coronary arteries and an old completely organized thrombus occluding the descending branch of the left coronary artery. The mouth of the right coronary artery was plugged by a recent embolus which, to all appearances, had come from a thrombus covering an atheromatous ulcer in the wall of the aorta just below the mouth of the artery.

The patient observed at the Johns Hopkins Hospital (Autopsy No. 15091) was a colored man about 24 years of age. He was dead when he arrived at the hospital. The heart was not enlarged and was grossly normal in appearance, but under the microscope there were many small scars in the right ventricle. The intima of the aorta was superficially roughened at a point a little above the orifice of the left coronary artery. Over this area of roughness there was a thrombus, the lower end of which projected into the mouth of the artery for the distance of a centimeter. There was another embolus in the right coronary artery, apparently a little older than the one in the left, since at one point there was beginning organization of the thrombus. Microscopic examination of the aorta demonstrated the characteristic changes of early syphilitic disease.

The six cases in this group were all men and five of them were relatively young, from 24 to 35 years of age. In four of these five the disease of the aorta upon which the thrombus formed was arteriosclerosis, in one it was syphilis. Only in the man of 72 years of age was there extensive sclerosis of the aorta; in the four other instances of arteriosclerosis, affecting younger men, the disease was localized. Plaques of arteriosclerosis in the aorta are not uncommon in persons from 30 to 40 years of age, and it is interesting to observe that occasionally coronary embolism may be the first and only symptom due to their presence.

3. *Coronary emboli coming from vegetations upon the heart valves*

The commonest source of coronary emboli is bacterial endocarditis. In the thirty-eight cases I have assembled, eighteen, or 50 per cent, be-

long to this group. Of the ten cases recorded at the Johns Hopkins Hospital, in six the embolus consisted of fragments of bacterial vegetations. Sometimes filamentous outgrowths of vegetations from the aortic valves wave about in the blood stream and may be floated into the mouth of a coronary artery; more often fragments of vegetations break off and are carried by a favoring current into the coronary circulation. These emboli, when big enough to plug large coronary vessels, are a not uncommon cause of sudden death in bacterial endocarditis. As I have said, these observations are matters of common knowledge and nothing further need be said about them.

4. *Coronary emboli coming from mural thrombi within the heart*

Dr. Garvin, the preceding speaker, has called our attention to the frequency with which mural thrombi occur in heart disease. In a consecutive series of 771 adults dying of heart disease, mural thrombi were found in 265, or over 34 per cent. Mural thrombi were found in the left side of the heart in 193 of the cases. I need only refer to what is already well known, namely, that the presence of these mural thrombi punctuates the course of heart disease with interesting and often dramatic symptoms. In the present relation, using Dr. Garvin's figures, I wish only to recall to your minds that in 25 per cent of all cases of heart disease there are mural thrombi in the left side of the heart, a condition threatening the occurrence of coronary embolism. These mural thrombi are friable, and small bits frequently break off and float free in the blood stream. These small emboli cause no symptoms or at most inconspicuous symptoms which we cannot ascribe confidently to embolism. Sometimes careful post-mortem examination will demonstrate to our surprise that they have occurred in great profusion, when clinically we have been unable to detect their presence. Less often, but still not infrequently, larger bits of the thrombus break off. However, even these usually pass unnoticed since most of them occlude arteries which are not end arteries or produce small infarcts in organs which give no signs of the loss of a small amount of tissue. Only when they are large enough to occlude big arteries or lodge in organs in which even relatively small infarcts produce grave symptoms do we become aware of their presence. The two organs most sensitive to infarction are the brain and the heart.

In heart disease evidence of cerebral embolism occurs commonly, of coronary embolism, infrequently. When we consider the size and position of the coronary arteries and the peculiarities of the coronary circulation, this relative incidence is not remarkable.

Among the thirty-eight assembled cases of coronary embolism, in five the embolus came from mural cardiac thrombi.

Rolleston in 1896 reported the case of a man, 17 years of age, who died suddenly. At autopsy an embolus was found in the descending branch of the left coronary artery. In the left ventricle there was a mural thrombus.

The patient of Gallaverdin and Dufourt was a man, 63 years of age, who died suddenly. The post-mortem examination revealed an embolus in the descending branch of the left coronary artery. There was an old myocardial scar with a mural thrombus.

Hadorn reports the case of a bicycle racer, 39 years of age, taken suddenly with severe pain in the left shoulder and arm, followed by severe vomiting. The pain persisted and later was located also beneath the sternum and over the upper portion of the abdomen. There were fever, shortness of breath and cough. Six days after onset he was admitted to the hospital with a diagnosis of pneumonia. The heart was enlarged, the sounds loud; there was a systolic murmur and the second pulmonary sound was accentuated. The patient was prostrated and short of breath. There were the usual signs of congestive failure. A pleural effusion on the right was tapped, and the fluid had the characteristic features of a transudate. The electrocardiogram was typical of anterior infarction. The patient improved somewhat but died suddenly fourteen days after the onset of the attack of pain. At autopsy the heart was found to be enlarged. There was a sero-fibrinous pericarditis. In the anterior portion of the left ventricle there was an infarct, at the apex an aneurysm, and mural thrombi in both ventricles. There was pronounced sclerosis of the coronary arteries. In the descending branch of the left coronary artery there was an old organizing thrombus; above this, plugging the mouth of the artery, there was a fresh embolus.

Two of the cases from the records of the Johns Hopkins Hospital fall into this group.

A colored man, 50 years of age, entered the hospital April 12, 1939 (History No. 138265), complaining of shortness of breath and palpitation of the heart. The symptoms had appeared two years before and had steadily become more and more pronounced. Four months before admission he had developed severe attacks of coughing accompanied by urgent dyspnea, and on one occasion the sputum had been bloody. These symptoms had gradually abated. Two days before admission he had been seized with severe pain in the epigastrium which radiated over the chest and down both arms. He had vomited frequently and had had great difficulty in getting his breath. The pain had persisted and was still present when he was admitted to the hospital but had gradually become less severe.

The patient was very ill, prostrated, drowsy, and sweating profusely. He was propped up in bed, and there was urgent dyspnea. The breathing was Cheyne-Stokes in character. The pupils were unequal and failed to react to light. The heart was very greatly enlarged, the rate rapid, the regular rhythm disturbed by the occurrence of occasional extrasystoles. The heart sounds were distant; a systolic murmur was heard at the apex; there was proto-diastolic gallop rhythm. The peripheral vessels were not much thickened; the blood pressure was low, systolic 102, diastolic 88, at admission. There were râles in the lower lobes of the lungs; the liver was moderately enlarged and tender.

The symptoms grew progressively worse. He had paroxysms of coughing with extreme dyspnea. He became mentally confused. There was mounting fever varying between 100° and 104° F. The leucocyte count was 10,000 on admission; it rose later to 32,000. On the fifth day after admission he complained of severe pain over the lower side of the chest and in the upper part of the abdomen on the right side. A friction rub and numerous coarse râles were heard in the lower axillary area, later also at the right base. Steadily he became more and more deeply prostrated, and died seven days after entering the hospital, nine days after the onset of severe pain.

The Wassermann reaction on the blood serum was negative. The electrocardiogram showed: first degree heart block; a marked levogram; T_1 inverted, T_2 iso-

electric, T_3 upright, inverted T of low amplitude in chest lead; $S\text{-}T_2$ and $_3$ slightly elevated; slurring and notching of QRS complexes; P waves abnormally large in Leads II, III, and V.

From these clinical data it was confidently assumed that the terminal symptoms were due to coronary occlusion and myocardial infarction. However there was much discussion about the nature of the preceding heart disease. Since the patient did finally develop coronary occlusion most observers favored the diagnosis of arteriosclerotic heart disease. Nevertheless, some pointed out the resemblance of the symptoms to those of syphilitic myocarditis, and the possibility of syphilitic myocarditis and of myocarditis of unknown etiology was seriously considered.

At the autopsy the heart was found to be enlarged, especially the left ventricle. The apex of the heart, including the left and the right ventricles, and the lower portion of the interventricular septum were infarcted. There were mural thrombi in both ventricles. In the anterior descending branch of the left coronary artery there was a thrombus occluding the lumen. Since there was very little sclerosis of the coronary arteries and none at the point where the thrombus was located, it was concluded that the thrombus had formed about an embolus coming from the mural thrombus in the left ventricle. Moreover, microscopic examination revealed that the thrombus was not attached to the wall of the artery. Scattered through the myocardium were interlacing scars and areas of cellular infiltration similar to those seen in syphilitic myocarditis. There was very little sclerotic change in the aorta and no evidence of syphilitic aortitis. Infarcts were present in the lungs and in the left kidney. The right renal artery was occluded by an embolus.

From the clinical and pathologic records of this patient we are justified in concluding that he had had some form of myocarditis, possibly syphilitic, and that a mural thrombus had formed within the left ventricle as often happens in this condition. A fragment from this thrombus had been swept into the left coronary artery, occluding the anterior descending branch and producing an infarct in the area of heart muscle supplied by the vessel. The following case is somewhat similar.

A negro woman, 39 years of age, entered the Johns Hopkins Hospital (History No. 144964) shortly after the onset of an attack of unconsciousness with convulsions. About an hour and a half before admission, while sitting quietly at her home, she suddenly began to shake all over and cried out that she could not walk. A few minutes later she lost the power of speech and a little later still became unconscious.

According to the history of her illness she had always been well until a year before admission to the hospital, when suddenly, while at work, a queer sensation had come on above the left ear. This was followed by vomiting which recurred during the next thirty-six hours. Shortly after the vomiting had begun, the right arm and leg had become paralyzed. Function soon returned in the leg, but the arm had remained weak for months. Five months before admission she had had an attack of transient loss of speech. From then on she had been weak; she had gradually lost thirty pounds in weight, and had complained frequently of headache.

Four months before admission to the hospital she had been examined in the outpatient department. She was described as a well-developed, well-nourished woman. The pupils were regular, equal, and reacted actively to light and on accommodation. The fundi were normal except for definite sclerotic changes in the retinal arteries. The heart was a little enlarged to the left; the sounds were clear; the second aortic sound was accentuated; there was gallop rhythm. The pulse was regular, the peripheral vessels moderately thickened, the blood pressure elevated, namely, systolic

207, diastolic 130. There was a mass in the lower abdomen arising from the pelvis, evidently a myomatous uterus. The neurologic examination was negative except that the knee jerks could not be obtained.

The blood count revealed a moderate degree of anemia. The Wassermann reaction was strongly positive. The urine contained a moderate amount of albumin. The electrocardiogram had the character of a levogram; there was normal sinus rhythm. T_1 was biphasic.

Upon admission to the hospital the patient was described as an obese woman in deep coma with noisy stertorous breathing. The pupils were dilated and fixed; there was external strabismus. The extremities were flaccid, the deep reflexes absent in the legs, sluggish in the arms; the Babinski test was positive on both sides. The lungs and heart could not be examined satisfactorily on account of the noisy breathing. The blood pressure was, systolic 220, diastolic 120. The spinal fluid was grossly bloody; the cell count gave 100,000 red corpuscles and 320 leucocytes, of which 68 per cent were polymorphonuclears.

After admission to the hospital the temperature rapidly rose and finally reached 109° F. The coma deepened, and the patient died ten hours after entry.

At autopsy the heart was found to be enlarged. Mural thrombi were present in both ventricles and in the right auricular appendage, and emboli were discovered in the basilar artery, the meningeal arteries, the left anterior cerebral artery, the splenic artery, and the coronary arteries. The coronary arteries showed small plaques of sclerosis here and there, but the degree of sclerosis was slight. Thrombi were found in the right coronary artery, and in the anterior descending branch of the left coronary artery, with infarctions at the apex of the heart and in the posterior portion of the ventricle behind the mitral valve. There was chronic passive congestion of the liver and conspicuous sclerosis of the arterioles in the kidneys, pancreas, and elsewhere.

In this patient no doubt enlargement of the heart had followed upon hypertension; as often happens, mural thrombi formed in the enlarged heart; from these thrombi had come the emboli which had lodged in the arteries of the brain, in the splenic artery, and in the coronary arteries

5. *Coronary emboli coming from thrombi in the pulmonary veins*

When we consider the great frequency of pulmonary infection we might anticipate that thrombosis of the pulmonary veins would occur commonly and that particles of clot dislodged from these thrombi would be a fertile source of embolic phenomena in the systemic circulation. However, experience teaches us that this is not the case. Embolism in pneumonia is very rare. The reason for this unexpected failure to observe the symptoms of embolism in pneumonia is the fact, well known to pathologists, that thrombosis of the pulmonary veins does not take place. Only when there is suppuration or invasion of the veins by tumor does thrombosis of the veins occur. In association with suppurative disease and carcinoma of the lung embolism is not uncommon; brain abscess in the one case and cerebral metastases in the other are frequent complications. Although venous thrombosis does not occur in uncomplicated pneumonia, nevertheless areas of suppuration frequently accompany and follow pneumonic inflammation, and it must be that often these areas are too small to be detected clinically and heal without the appear-

ance of betraying symptoms. Therefore I remain surprised at the infrequency of embolic manifestations in the course of pneumonia. I know of only two instances in which an embolus plugging a branch of a coronary artery has been demonstrated to have come from the pulmonary veins.

Medlar reports the post-mortem studies on a man, 40 years of age, who had been ill with pulmonary tuberculosis for six months, yet not ill enough to have been confined to bed. On the day of death he was up and about as usual. While walking he collapsed and died immediately. The autopsy revealed bilateral pulmonary tuberculosis and a small cavity in the right upper lobe. There was recent infarction of the lateral and upper portion of the left ventricle, the infarct measuring 3 cm. in length and 1.5 cm. in width. The valves of the heart and the endocardium were normal. The coronary arteries were healthy. No thrombus was discovered on gross inspection. Microscopic examination of sections disclosed in the neighborhood of the infarcted area a branch of the coronary artery plugged by a mass of caseous material containing numerous tubercle bacilli. There was no evidence of tuberculosis in the tissues about the artery, and tubercle bacilli could not be found in these tissues.

The case observed at the Johns Hopkins Hospital is unusually interesting and apparently unique; therefore I report the records in greater detail.

A white man, an engine stoker, 57 years of age, entered the Johns Hopkins Hospital Oct. 18, 1932 (History No. 45924), complaining of weakness and stomach trouble. Until three years before, when his illness had begun, he always had been a strong, healthy man, boasting that he had never been sick a day in his life. The illness had come on suddenly. One afternoon, probably an hour after his midday meal, suddenly he was seized with excruciating pain in the abdomen just below the xiphoid cartilage. He sweated so profusely that his clothes were soaking wet. The pain continued the whole afternoon and was so severe that he was like a "crazy man" as he expressed it. At 9 o'clock that evening a physician arrived who gave him two hypodermics, but with relatively little benefit. The pain continued during the night until the following morning at four o'clock, when he vomited profusely, and after this he felt immediate relief. Preceding the vomiting the abdomen had been blown up with gas. Following this event he had some fever and was very much prostrated. He was obliged to remain in bed for four weeks. When he got up he went about quietly for another week and then returned to work. His work was heavy, and he had great difficulty in carrying it on because he felt very weak, and also now for the first time he began to notice marked shortness of breath on effort. After a few weeks he was obliged to give up. He tried again and again to work but on each occasion he could keep at it for only a week or two, and then he had to stop on account of weakness and shortness of breath. A few months before coming to the hospital he had caught a cold. This brought on cough with dark sputum which often was streaked with blood. The cough continued, his shortness of breath grew worse, and he had been obliged to spend most of his time in bed.

Examination.—His temperature was 100.4° F., pulse, 76, respiration 22, blood pressure, 126/100. The patient was a fairly well-nourished man who evidently had lost much weight. He was propped up in bed with moderate dyspnea. He had frequent attacks of coughing but raised very little expectoration. The skin and mucous membranes were rather pale. The eyes were normally prominent. The extraocular movements were normal. Pupils were equal, regular, reacted actively to light and on accommodation. The fundi showed practically normal conditions,

only a slight degree of sclerotic change in the arteries. The teeth were worn and many were carious; there were a number of old stumps. The gums were in fairly good condition. The throat showed nothing remarkable. A number of the cervical and axillary lymph nodes were palpable, but there was no marked lymph node enlargement. The thyroid was of average size and normal consistency. The chest was long and narrow with diminished expansion on the right side. On the right there was flatness below the level of the fourth rib in front and below the angle of the scapula in back. Over this area the breath sounds were greatly diminished in intensity, and there was typical egophony. At the upper border of dullness the breath sounds were tubular in quality, and many moist râles were heard. The apex beat of the heart was in the fifth intercostal space, 11 cm. from the midline. Cardiac dullness to the right could not be ascertained on account of the pulmonary dullness. It extended 13 cm. to the left. The heart sounds were clear; the second aortic was louder than the second pulmonic. The pulse was equal at the two wrists. The vessel walls were moderately thickened. The blood pressure varied a little in the two arms—right 112/84; left 126/100. The abdomen was distended. It moved freely with respiration. A mass was felt in the right upper quadrant extending 6 cm. below the costal margin. This seemed certainly to be the liver although a lower border could not be felt on account of the tenseness of the abdominal wall. There was edema of the ankles and over the tibiae up to the knees. There was a little edema over the sacrum. Genitalia showed no abnormality except slight edema of the scrotum and prepuce. Rectal examination showed an enlarged, hard prostate but otherwise was negative. Neurologic examination revealed no abnormality.

Course in the Hospital.—The right pleural cavity was tapped on the day of admission, and 1300 c.c. of cloudy fluid were withdrawn. Following this the patient was more comfortable. The physical signs over the right lower lobe now suggested that there was consolidation of the lung as well as pleural effusion, and a roentgenogram taken two days later confirmed this impression. The fluid recurred promptly and the pleural cavity frequently was tapped. All of those who examined the patient thought there was evidence of pulmonary infiltration as well as of fluid at the right base. This pulmonary infiltration was thought to be either carcinoma or pulmonary infarction. The roentgenogram at first favored the diagnosis of carcinoma but the shadow gradually decreased in size and finally almost completely disappeared. The physical signs over the chest also changed; at the beginning of December there were only dullness and diminution in the intensity of the breath sounds over the right lower lobe. With this improvement in the pulmonary condition there was simultaneous improvement in his general condition. He gradually lost his dyspnea and by the beginning of December he felt so well that he was eager to be out of bed. The wide area of cardiac dullness to the left, present when the patient entered the hospital, was due apparently to dislocation of the heart to the left by the pleural effusion. After the effusion disappeared the heart returned to its normal position but was still definitely enlarged. From time to time the heart's action was irregular due to the occurrence of numerous extrasystoles. During the first month that the patient was in the hospital he had a good deal of cough and raised small amounts of mucoid sputum which frequently was streaked with blood. On Dec. 16, 1932, the note was made "the patient is much improved and is getting up as desired." He still had some cough but very little sputum. There were still dullness and diminution in intensity of the breath sounds over the right lower lobe. A little swelling of the ankles persisted.

On the morning of Dec. 20, the patient awoke with rather severe pain over the heart and shortness of breath. The symptoms of myocardial insufficiency recurred and grew gradually more and more severe during the day. A proto-diastolic gallop was heard at the apex; the heart sounds were distant and feeble; the pulse was thready and the blood pressure fell to systolic 90, diastolic 60. A definite pleural friction was heard over the front of the left chest. During the next night he be-

came progressively worse. His pulse became weaker, his respirations very irregular and gasping. There was extreme cyanosis; his face looked drawn and had an ashen hue. He sweated profusely. On the morning of Dec. 21, he was pulseless and comatose. The friction rub over the left lower chest became more pronounced and breath sounds in that area were suppressed. His condition grew steadily worse; the pulse disappeared at the wrist and the blood pressure was so low it could not be estimated. A little after midnight on Dec. 22 he died quietly.

The blood counts were normal. The Wassermann reaction was negative. The urine on admission had a normal range of specific gravity; it contained a large amount of albumin and many casts. Later albumin disappeared and only an occasional cast was found. The electrocardiograms showed sinus rhythm, usually regular, at times disturbed by ventricular extrasystoles; delayed auriculoventricular and intraventricular conduction, left bundle branch block. The measurements of the teleroentgenogram were: M. R. 9; M. L. 9.3; A. 9.2; T. 28.7.

From the autopsy record the following excerpts are made:

Anatomic Diagnosis.—Thrombosis of anterior descending branch of left coronary artery. Scarring of myocardium. Scarred sacculated infarct of left ventricle covered by large thrombus somewhat organized. Thrombus at tip of right ventricle. Cardiac hypertrophy and dilatation. Pericardial adhesions at apex. Thrombi in branches of pulmonary artery, right and left lower lobes. Infarcts in lungs. Hydrothorax left, 400 c.c. Chronic passive congestion of lungs, liver, and spleen. Lobular pneumonia. Empyema at the base. Arteriosclerosis of aorta. Atrophy and scarring of pancreas. Slight scarring of kidneys. Enlargement of thyroid with colloid adenomata. Benign prostatic hypertrophy, slight. Caseous lymph nodes at hilum of right lung. Pleural adhesions, right. Hemorrhoids, internal.

The heart is enlarged, the enlargement due chiefly to dilatation of left ventricle. Weight was 600 grams. Epicardium is smooth and glistening except over the apex where there are dense adhesions between the layers of the pericardium over an area about 3 by 4 cm. on the anterior surface of the left ventricle. Almost the entire wall of the left ventricle anteriorly is covered by a large thrombus which at the apex measures 3 cm. in thickness. This appears to be relatively old and undergoing organization. At the tip of the right ventricle a fresher thrombus is adherent to the endocardium, measuring 1.5 by 1 cm. The valves are all delicate and competent. The myocardium contains a few small scars near the base. At the apex of the left ventricle the wall is distinctly thinned and the myocardium appears to be replaced by dense fibrotic tissue. This covers practically all of the apex and extends upward about halfway to the base of the heart. The right ventricle appears to be normal except for a small area at its tip which is covered by the small thrombus mentioned above. The mouths of the coronary arteries are not obstructed. About 2 cm. from the origin of the anterior descending branch of the left coronary there is an old thrombus apparently undergoing organization. It practically occludes the lumen of the artery. No sclerosis of the coronary arteries is anywhere visible, and the arteries are delicate and straight.

The left lung weighs 750 grams. Its external surface is smooth and normal in appearance. At the tip of the lower lobe, anteriorly, there is a thrombus in the small branch of the pulmonary artery leading to a fresh infarct; elsewhere the lung is air-containing and normal in appearance. The right lung is removed with difficulty because of firm adhesions to the diaphragm and costal pleura, and the posterior portion of the lower lobe is torn away and left firmly attached to its overlying pleura. The pleura in this area is greatly thickened and between its layers is a collection of about

25 c.c. of pus. The upper and middle lobes show nothing abnormal on section. The posterior portion of the lower lobe does not contain air. It is black in color and rubbery in consistency. A large branch of the pulmonary artery leading to it is found to contain a rather old thrombus, organizing and extending 3 or 4 cm. along its course. About the bronchi there is a collection of moderately enlarged lymph nodes which show patches of calcification on section.

Microscopic notes.—Section through the coronary artery shows a perfectly normal delicate structure without arteriosclerosis. A section taken a little further down shows a partly organized thrombus which nearly occludes the lumen of the artery.

A section taken through the wall of the left ventricle shows marked scarring of the myocardium with gradual dwindling of the muscle fibers as the thrombosed area is approached, where the scarring becomes more pronounced. Finally the muscle fibers are replaced by a firm dense scar over which lies the old thrombus now become fairly well organized and laminated and covered with a fresher thrombus. Section taken through the mitral valve shows some hypertrophy of muscle fibers and some slight scarring of the myocardium. The valve, the epicardium, and endocardium are normal.

One section of the lung shows an organized thrombus in the branch of the pulmonary artery; another section shows a hemorrhagic infarct. In other places there are areas of lobular pneumonia which contain Gram-positive diplococci. There is marked chronic passive congestion of the lung and many alveoli are filled with mononuclear cells containing blood pigment. Another section shows an old abscess, very well encapsulated between the two layers of the pleura. There is some organization.

In this instance the evidence that the coronary occlusion was due to an embolus and not to arteriosclerosis seems to me to be incontrovertible. No origin for the embolus was found other than the pulmonary abscess, and since the existence of a relation between the two is an altogether reasonable supposition, we are warranted in assuming that the embolus came from that source.

6. *Coronary emboli coming from thrombi in the systemic veins*

Paradoxical embolism does not occur frequently; therefore, I was surprised to find it reported four times among the thirty-eight collected cases of coronary embolism, an incidence of over 10 per cent. It is unbelievable that this high incidence represents a true proportion, and no doubt it is explained by the fact that, since paradoxical embolism is rare, most instances that are observed are reported, whereas commoner forms of coronary embolism are not deemed worthy of such particular notice.

Wolff and White mention the case of a woman, 43 years of age, with carcinoma of the ovaries. Suddenly she fainted and shortly after died. Autopsy revealed thrombosis of the pelvic veins, embolism of a patent foramen ovale, and embolism of the descending branch of the left coronary artery.

Thompson and Evans report about a young man, 25 years of age. Five days before entering the hospital, while at work, suddenly he had fallen unconscious and thereafter had never properly rallied. He died about half an hour after admission to the hospital. The hasty examination disclosed coma, stertorous breathing, left hemiplegia. At the post mortem there were a malignant teratoma involving both testes; a mass of growth projecting through the patent foramen ovale; a large

polypoid mass of growth projecting from the wall of the left ventricle and a similar mass free in the left ventricular cavity; growth emboli in both coronary arteries and in the right middle cerebral artery.

Saphir reports the case of a man, 35 years of age, admitted to the hospital with bronchopneumonia. The pneumonia spread and auricular fibrillation came on. A few days later the right femoral artery became occluded followed by gangrene of the foot. At the end of three weeks the leg was amputated between the middle and lower third of the femur. The patient recovered from the operation and convalescence was proceeding uneventfully when on the seventeenth postoperative day he died suddenly.

At the autopsy was found diffuse sclerosis of the aorta. At the bifurcation there was an atheromatous ulcer covered by a thrombus. An embolus completely occluded the right femoral artery. The right femoral vein was filled with thrombus which extended into the iliac vein. The heart was enlarged. The right auricle contained an embolus which extended into the right ventricular cavity. The foramen ovale was patent. An embolus occluded the descending branch of the left coronary artery. The intima of the coronary arteries was smooth, without evidence of sclerosis. In the lungs there was organizing bronchopneumonia. Many of the smaller branches of the pulmonary artery in both lungs were plugged by emboli.

The patient reported upon by Mendel, Kenler and Silverman was a woman, 47 years of age. Six days before admission to the hospital she had been taken ill with vague pains and aches diagnosed as grip. A few days later she developed vomiting, diarrhea, and abdominal cramps. She was a well-developed, well-nourished woman. The physical examination revealed no noteworthy abnormality. There were no cardiovascular symptoms and the heart was quite normal. On the sixth day in hospital she was seized suddenly with sharp, agonizing pain under the sternum and fifteen minutes later was dead.

At the post-mortem examination the heart appeared to be normal except that the foramen ovale was patent, the opening measuring 0.5 cm. in diameter. The valves were unaffected, and there were no thrombi in auricles or ventricles. The anterior descending branch of the left coronary artery was occluded by a soft lamellated gray-red thrombus, 1 cm. in length and 0.3 cm. in diameter. The thrombus was easily removed, disclosing the underlying intima which was smooth, glistening, and utterly devoid of atheromatous change. The coronary arteries throughout the heart were equally normal in appearance. In the aorta there were a few small yellowish patches of atheroma, but the intima over these, as elsewhere, was smooth and glistening. There was no slightest evidence of syphilis. The left femoral vein was plugged by a firm brownish clot which at its proximal end, near the entrance to the iliac vein, was continued as a grayish-red softer thrombus, similar in appearance to the one found in the coronary artery. There was slight pitting edema over the whole left leg and the sacrum, a fact which had been overlooked clinically.

The Clinical Features of Coronary Occlusion Produced by Large Coronary Emboli

From this brief review of observed cases of coronary embolism it is apparent that the symptoms of this condition are characteristic of those of coronary occlusion from whatever cause. It would be impossible even to venture the diagnosis from any particular differences in the symptoms. There is only one special feature that has been commented upon, namely, that in most cases death is very sudden, indeed instantaneous. This is explained by the fact that coronary embolism has no rela-

tion to disease of the coronary arteries and therefore will occur often when the coronary arteries are healthy and the heart unprepared, by the gradual development of an efficient collateral circulation, to withstand the effects of occlusion of a large branch. Nevertheless this feature is not sufficiently distinctive to be helpful in diagnosis. For purposes of diagnosis we must depend upon suggestions that may come from the whole clinical setting in which the accident occurs.

One of the important elements of this setting is the age of the patient. Coronary thrombosis secondary to atherosclerosis occurs seldom before forty years of age. I am well aware of the fact that a large number of cases are now on record which have come on in the thirties and many even in the twenties. However, cases occurring at an early age attract comment and are often reported. In the hope that I might find evidence to justify the suspicion that some of the cases of coronary occlusion affecting young persons may have been due to embolism and not to arteriosclerosis, I reviewed the details of many records in the literature. I was unable to find the evidence I sought. Many of the patients recovered and although the clinical records left no reasonable doubt about the accuracy of the diagnosis of coronary occlusion, still, in the absence of anatomic study, the nature of the mechanism of occlusion could only be surmised. In another large group of cases, the post-mortem findings are only briefly and incompletely reported so that the cause of the occlusion is not clearly demonstrated. In the remaining cases the results of the autopsy are given in sufficient detail to establish with reasonable security that the cause of the occlusion was coronary arteriosclerosis. Nevertheless it must be admitted that even anatomically the diagnosis of coronary embolism is difficult and that only rarely will it be made unless the evidence supporting that diagnosis is carefully searched for. The experience at the Johns Hopkins Hospital recurs to me again. Judging from the records of the Pathologic Department the diagnosis was not recorded during a period of over fifty years, but once having been made it was repeated ten times during the following nine years. Therefore it is reasonable to anticipate that when pathologists examine cases of coronary occlusion with the possibility of embolism prominently in mind, more and more instances of this condition will be recognized.

The occurrence of coronary embolism when the embolus is a thrombus or atheromatous material from the coronary artery itself has no clinical interest. Coronary occlusion due to emboli coming from thrombi covering plaques of sclerosis in the wall of the aorta presents an almost impossible problem in diagnosis. Five of the six patients reported were from 24 to 35 years of age, averaging 30 years. Sudden death occurring in a young person who had previously been healthy might awaken a suspicion of coronary embolism from that source but the diagnosis could not be differentiated from coronary thrombosis due to coronary sclerosis. Coronary embolism would be suggested immediately were a patient with bacterial endocarditis to die suddenly. Sudden death in bacterial endo-

carditis is usually due to coronary embolism or the rupture of a mycotic aneurysm into the pericardial cavity but sometimes even at autopsy no gross cause for the sudden death is discovered. Cerebral embolism or the rupture of a mycotic aneurysm elsewhere than into the pericardial cavity is seldom instantaneously fatal. If from the clinical manifestations we are able to conclude that a patient with heart disease has a mural thrombus within the left auricle or ventricle we would suspect that coronary embolism had occurred were he to die suddenly. I have already expressed surprise that coronary emboli coming from thrombi in the pulmonary veins have been observed so very seldom. On a number of occasions I have examined patients in the thirties or early forties who have had coronary occlusion followed by perfect and long continued recovery and have suspected that the occlusion may have been due to an embolus coming from this source. However, no confirmation of the supposition could be obtained. Perhaps more cases will be found when they are carefully looked for. Coronary embolism might be predicted in a patient having thrombophlebitis and dying with the characteristic symptoms of coronary occlusion. However, a confident distinction from pulmonary embolism would be difficult.

Although to diagnose coronary embolism correctly might confer academic satisfaction and distinction, it is pertinent to ask what consequences of benefit to the patient could possibly follow from the diagnosis. As far as I can see there is only one. I have already commented upon the fact that when an embolus occludes a large branch of a coronary artery, death is usually instantaneous because the coronary arteries are healthy; for the same reason if a patient recovers from the effects of coronary embolism the chances are good that recovery will be complete and permanent, for there is no reason to fear a repetition of the accident, and the remaining heart muscle is healthy and abundantly nourished. In a word, whereas the immediate prognosis is bad, if the patient lives the ultimate prognosis is good. This being the case, were we able to say with assurance that coronary occlusion had been due to embolism we could look to the future with encouraging confidence, and restrictions upon activity need be less severe.

At the present time the diagnosis of coronary embolism is extraordinarily difficult and I doubt that it can be made definitely except under unusual circumstances. Nevertheless if in differential diagnosis we bear it in mind we shall see many cases in which this possibility must be carefully considered and perhaps in time we may learn to recognize distinguishing features. To make my meaning clear I shall cite an illustrative case.*

In November, 1938, I saw upon the wards of the Cincinnati General Hospital, with Dr. Marion A. Blankenhorn and Dr. Johnson McGuire, a young woman, 34 years of age, who was in the fifth month of pregnancy. She was an overnourished

*I am indebted to Dr. Blankenhorn for permission to report this case and to Dr. W. B. Bean for a summary of the hospital records.

woman having the appearance of robust, vigorous health. She felt well and the physical examination revealed no abnormality. The heart was not enlarged; the sounds were clear and of normal quality except for the presence of a soft systolic murmur. The pulse was slow and regular, the peripheral vessels soft, the blood pressure, systolic 132, diastolic 60. The electrocardiogram was essentially normal. The patient had been admitted to the hospital for a decision upon the advisability of interrupting pregnancy. In order to appreciate the pertinency of this question it is necessary briefly to review the records of previous admissions to the hospital.

March 30, 1927, admitted to the obstetrical service and the following day was delivered spontaneously of a healthy child.

Aug. 10, 1928, again admitted to the obstetrical service and the same day gave birth spontaneously to a healthy child. During the latter months of pregnancy had had a little edema of the ankles and a little shortness of breath.

On Dec. 25, 1930, was admitted to the surgical service. A diagnosis of gall stones and cholecystitis was made. On this occasion as well as on the two previous admissions no evidence was found of the slightest abnormality in the heart. Patient left the hospital but a little later cholecystectomy was performed at another hospital.

April 8, 1937, she entered the hospital on the medical service complaining of shortness of breath, cough, and swelling of the ankles. She had been well until eleven days before admission when she began to have pain in the right upper quadrant of the abdomen. She felt chilly and later feverish. The following day the pain spread over the front of the chest on both sides and cough and expectoration developed. On the fifth day after the onset of the illness, at a time when she was still in bed, though feeling much better, she was suddenly taken with severe shortness of breath and palpitation. The dyspnea steadily increased; she had paroxysms of coughing and raised frothy expectoration; later edema appeared about the ankles and gradually spread to the legs.

On admission the temperature was 99.6° F., the pulse 106, the respirations 30, the blood pressure 158/124. She was a well-developed and well-nourished woman propped up in bed, with great shortness of breath. The apex beat of the heart was in the sixth intercostal space 10 cm. to the left of the midline. The area of cardiac dullness measured 3.5 cm. to the right and 10.5 cm. to the left. The heart sounds were described as being of poor quality and some observers heard a soft systolic murmur. There was decided proto-diastolic gallop rhythm. The pulse was regular, the peripheral vessels soft, only slight arterial changes in the ocular fundi. The peripheral veins were distended, and there was slight cyanosis. The legs were swollen with edema. Numerous moist râles were present over the lower lobes of the lungs and at the right base there were signs of consolidation. The liver was a little swollen and tender.

Under treatment with digitalis the edema and shortness of breath soon disappeared, the slightly elevated temperature fell to normal, and the signs of consolidation at the right base cleared. Successive electrocardiograms revealed changes characteristic of an anterior infarction.

The patient left the hospital without symptoms and in good condition.

For a year after discharge from the hospital she continued to take digitalis and during this period led an active life and was well. At the end of the year there seemed to her to be no reason for continuing digitalis, and therefore she stopped taking it. Late in June or early in July, 1938, she became pregnant and when she appeared at the prenatal clinic in October, her previous records were reviewed, and on account of the symptoms of heart failure that had been observed and diagnosed as coronary occlusion during her stay in the hospital a year and a half before, she was again admitted for consideration of the advisability of interrupting the pregnancy.

With these records and observations before us the diagnostic problem was an interesting one. A healthy young woman, 33 years of age, during the course of a respiratory infection is taken suddenly with severe shortness of breath and palpitation followed by the typical symptoms of congestive failure. These symptoms soon subside and recovery is seemingly complete since the patient was able to lead a very active life without the least discomfort. A number of examinations made before the attack of heart failure had occurred, and a very thorough investigation made a year and a half after the attack, had failed to show the slightest evidence of disease of the heart. This brief period of heart failure in a healthy young woman, coming on abruptly and leaving after it no sign of permanent damage to the heart, can best be explained as evidence of coronary occlusion. The electrocardiographic changes support this conclusion. Therefore assuming that the patient had had coronary occlusion we stopped to consider the cause of the occlusion. There was no direct evidence to justify a diagnosis of coronary arteriosclerosis, and yet it is well known that even advanced coronary arteriosclerosis may exist in the absence of any signs that might betray its presence. Moreover coronary sclerosis need not be advanced to cause occlusion of an arterial branch; thrombosis may follow the rupture of an isolated atheromatous ulcer and the rest of the coronary arteries show only insignificant change. Nevertheless under the circumstances it was not unreasonable seriously to consider the possibility that the occlusion might have been caused by an embolus. The fact that the cardiac symptoms had come on suddenly as an acute respiratory infection was subsiding suggested that the embolus, if it was an embolus, had come from a thrombus in the pulmonary veins. Could one be sure that the occlusion had been caused by an embolus there would be no threat of further damage to the heart and with this assurance there could be no hesitation in deciding to allow the pregnancy to proceed. I do not mean to imply that considering all of the circumstances the decision necessarily would have been in favor of terminating the pregnancy had it been possible to establish the diagnosis of coronary thrombosis on the basis of arteriosclerosis, but merely that the possibility of coronary embolism was a factor in arriving at the conservative decision.

The pregnancy proceeded uneventfully, and on March 31, 1939, the patient was delivered of a healthy, full-term child. Since leaving the hospital she has been observed regularly in the cardiac clinic. She has remained well, and no slightest abnormality has been detected in the circulatory system.

I wish to emphasize that I report this case not as an instance of coronary embolism but merely as an illustration of the sort of circumstances under which the possibility of coronary embolism should seriously be considered.

II. CORONARY EMBOLI OCCLUDING SMALL BRANCHES OF THE CORONARY ARTERIES

The occlusion of small branches of the coronary arteries produces scarring of the heart, and if many small branches are occluded, the scarring may become widespread and seriously impair cardiac efficiency. In contrast to the dramatic symptoms which usually follow occlusion of large coronary branches, the obstruction of small branches proceeds unnoticed. Only after large portions of the heart muscle have been destroyed, do symptoms appear, and these symptoms are the usual ones of heart failure which are in no way distinctive of coronary disease. The diagnosis of myocardial scarring due to coronary disease is reached by a circuitous path of reasoning and inference. In the presence of heart failure, to begin with, we must eliminate valvular defects, hypertension in the general circulation and in the pulmonary circulation, pericardial adhesions or effusion, and congenital anomalies as the cause of the failure. If by this process of elimination we arrive at the conclusion that disease of the heart muscle is the essential cause we must then proceed by a careful consideration of all the evidence at hand to decide upon the nature of the underlying myocardial disease. In the absence of heart failure certain disturbances of rhythm, for instance heart block, and abnormalities in the electrocardiogram furnish important evidence of damage to the heart muscle. After we are reasonably sure that the heart muscle is seriously injured and that the cause of the injury is impairment of the coronary circulation, we may then attempt to decide whether the impairment is due to diffuse coronary arteriosclerosis or to the obliteration of many small coronary branches by emboli. In reaching this final decision we are guided not only by an examination of the circulatory system but also by a careful consideration of all the associated manifestations of the illness. The two conditions with which we observe multiple coronary emboli are bacterial endocarditis and intracardiac thrombi.

I have pointed out that bacterial endocarditis is the usual source of emboli which plug large branches of the coronary arteries. However, such large emboli lodge in the coronary arteries in only a relatively small number of the cases. In contrast to this, numerous small emboli enter the coronary circulation almost invariably. Evidence of their presence is seldom missed when sections of the heart muscle are examined under the microscope. Recently de Navasques very thoroughly studied the hearts from twenty cases of *Streptococcus viridans* endocarditis. In all but one he found evidence of coronary embolism. Saphir reports finding small organizing infarcts in twenty-eight of thirty-five unselected cases.

These small coronary emboli produce no symptoms by which their presence may be recognized. Apparently they bear no definite relation to the degree of myocardial insufficiency. Patients with bacterial endocarditis usually die of the infection or complications, seldom of myo-

cardial insufficiency. In the rare cases in which death is caused by heart failure it would be interesting to examine carefully the heart muscle to determine to what extent myocardial damage, due to coronary emboli, had contributed to the failure.

I have already cited the figures of Garvin indicating that at autopsy mural thrombi are found in the left side of the heart in 25 per cent of all cases in which death is caused by heart failure. Clinicians are thoroughly familiar with the embolic manifestations that come from these thrombi and guided by these symptoms are able to predict their presence. As I have pointed out, large emboli occasionally lodge in the coronary arteries, producing the characteristic symptoms of coronary occlusion. In a large number of the cases small emboli reach the coronary circulation and sometimes in such profusion as seriously to damage the myocardium and in this way precipitate heart failure. It is true that there must be some antecedent disease of the heart for mural thrombi to form, but often this disease is of a nature not seriously to impair its function. The symptoms of heart disease and the final failure may all be due to the emboli discharged from the mural thrombus. Clinicians seem not fully to have realized the importance of numerous small coronary emboli as a cause of heart failure. At the Johns Hopkins Hospital the matter has been called to our attention again and again by Dr. Rich at clinical-pathologic conferences, and during the past few years on a number of occasions we have correctly predicted that the autopsy would reveal the presence of these lesions.

In describing large coronary emboli coming from mural thrombi I cited a case of multiple infarcts of the heart. In concluding I will report briefly another instance in which numerous small emboli led to extensive myocardial fibrosis.

A Polish steel worker, 45 years of age, entered the Johns Hopkins Hospital Jan. 27, 1939 (History No. 162602), complaining of pain in the abdomen and over the heart. Three years before over a period of a month he had complained constantly of pain about the heart. There had been no other symptoms. His physician had told him his heart was enlarged. In other respects he had always been well. The illness that brought him to the hospital had begun three months before, when he had been taken suddenly with severe pain in the right lower quadrant of the abdomen. He had entered the Church Home and Infirmary where his appendix had been removed. He made an uneventful recovery and returned to his work. Two weeks before admission he began to have pain in the upper part of the abdomen and also over the heart. The pain had continued intermittently. With the onset of pain there had been shortness of breath, and this gradually had become more and more severe. The important points in the physical examination were these: Well-developed man of healthy appearance, moderately dyspneic. Only a little cyanosis. The heart was considerably enlarged, particularly to the left. The heart sounds were distant and faint but no murmurs were heard. There was definite gallop rhythm. Pulse was regular, rapid, of small size. No evidence of sclerosis of the peripheral or retinal arteries. Râles of edema over the lower lobes of the lungs, an enlarged tender liver, and a little subcutaneous edema at the ankles and over the sacrum.

The patient spent four months in the hospital. He improved very slowly. On March 24, he had an attack of weakness and dizziness followed by a period of mental confusion. On discharge from the hospital on May 28, 1939, he was somewhat better but it was clear that he had little cardiac reserve. The blood pressure was systolic 115 to 154, diastolic 95 to 124. The pulse pressure was always low. The electrocardiogram on admission showed a levogram with tendency towards low voltage. T_1 and $_2$ were inverted. There was slurring of QRS_1 and $_2$.

Patient entered the hospital again Dec. 12, 1939. During the seven months intervening between his previous discharge and this admission the patient had got on reasonably well but was always short of breath and complained often of pain about the heart. Early in November distressing attacks of nocturnal dyspnea had begun to occur. From then on there was increasing shortness of breath and later swelling of the ankles. The examination on this occasion showed decided dyspnea and cyanosis was pronounced. The veins in the neck were engorged. The heart was more enlarged than on the previous admission, the heart sounds were faint; no murmurs were heard; the second pulmonary sound was accentuated. Pulse was regular and rapid; there was no unusual sclerosis of the peripheral or retinal vessels. Râles of edema were heard over the lower lobes of the lung, and in the right pleural cavity there was a small effusion. There was now definite ascites. The liver was swollen.

After admission to the hospital the patient had considerable fever for which no explanation was found. He was always short of breath and complained of pain over the engorged liver. The venous pressure was 250 mm. of water, on another occasion 276. The patient was delirious and the delirium became more pronounced. On Dec. 30 it was noticed that the left leg was cold below the knee and the skin mottled. No pulsation could be felt in the arteries of the leg. From then on Cheyne-Stokes breathing became more pronounced with long periods of apnea, the lungs filled with coarse bubbling râles and the following day, Jan. 1, 1940, the patient died.

The important facts from the records of the autopsy are as follows:

Anatomic Diagnosis.—Moderate generalized and coronary arteriosclerosis. Diffuse myocardial scarring. Mural thrombus left ventricle. Cardiac hypertrophy and dilatation. Multiple emboli, left femoral, mesenteric, right renal, cerebral and pulmonary arteries. Old and recent infarcts of spleen. Recent infarct of right kidney. Encephalomalacia. Purulent bronchitis and lobular pneumonia, lower lobes of both lungs.

The heart is moderately enlarged, weighing 590 grams. Left side dilated and hypertrophied, right side dilated. The epicardium is smooth. Valves are all delicate and competent. In the left ventricle is a large, oval thrombus attached to the interventricular septum, extending upward from the apex for a distance of about 7 cm. The musculature of the left ventricle is firm except that in the posterior wall there are areas of contrasting softness. In the root and ascending arch of the aorta there are a few small sclerotic plaques which do not encroach upon the mouths of the coronary arteries. The large branches of the coronary arteries show a few small scattered arteriosclerotic plaques. There is no narrowing of the lumen of the arteries. The right coronary artery is somewhat longer and wider than usual and it is somewhat more sclerotic than the left.

Microscopic Notes.—All the sections of the heart show rather pronounced myocardial scarring. This is of two distinct types, one diffuse and consisting of strands of scar tissue between muscle fibers, the other circumscribed and consisting of large areas in which the muscle tissue has been replaced by scar tissue. Near these large scars occluded blood vessels are seen, the occlusion probably due to emboli.

Several sections of the right and left coronary arteries show a moderate degree of sclerosis with thickening of the wall but only slight narrowing of the lumen.

The heart of this patient showed diffuse interlacing scar tissue, evidently the result of a preceding myocarditis of unknown etiology. The myocarditis was the primary disease but since at autopsy only diffuse scarring remained to reveal that it had been present it evidently was not responsible for the heart failure. Once the thrombus had formed in the left ventricle it became the source of subsequent symptoms; not only of the numerous embolic manifestations that occurred, but also of the heart failure itself which undoubtedly was due, at least chiefly, to numerous small coronary emboli.

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BLOOD VOLUME AND CARDIOVASCULAR ADJUSTMENTS

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I MUCH appreciate the honor of succeeding my two distinguished predecessors in this lectureship. Both of your previous lecturers have considered problems involving fluid balance. Today I propose to consider the blood in its relation to the circulation. Certain simple axioms may be stated—so simple that we shall all be in agreement. Certain definite clinical facts are established. Beyond these we pass into a region of conjecture and hypothesis, where our knowledge is very incomplete. In this field, clinical observation and physiologic investigation may together clarify the situation, but either of these alone has little chance of finding any real solution.

The most obvious axiom is the fact that the blood volume and the capacity of the vascular bed must always be the same. The elastic vascular bed may be distended at a greater or less pressure, but empty spaces are unthinkable. We are all familiar with the marked variations in vascular tone, of shorter or longer duration, that may develop. We are all likely to forget that any such change in the size of the vessels must be associated with a corresponding change in blood volume, unless the circulatory system is so regulated that any enlargement of one set of vessels is exactly balanced by an equal reduction in the size of other vessels. Although such a reflex control does probably play the major role in rapid adjustments, alterations in blood volume appear to be part of the normal mechanism. These alterations in blood volume are to meet the demands of an altered vascular bed.

We may also accept as axiomatic Starling's[1] hypothesis of fluid balance. The osmotic forces exerted by colloidal plasma proteins which attract fluid into the capillaries balance the filtrating forces created by capillary pressure. More recent investigations of this balance from very different angles include work by Landis[2] and Gregersen and Stewart.[3] In the past, tissue fluid pressure has been considered negligible; at the present time we know that this is not the case.[4] The differences in hydrostatic pressure between the capillaries and the tissue spaces are none the less balanced by the differences in colloidal osmotic pressure between the plasma and tissue fluid. With this slight modification, Starling's hypothesis still stands, and it seems unlikely that it will ever be seriously challenged. On Starling's hypothesis, the volume of the blood plasma is determined by the total amount of plasma proteins

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circulating in the vessels, for this quantity determines the volume of fluid that can be maintained in the system with a balance at a normal pressure level. We know full well that, after a moderately large hemorrhage, this quantity of protein is reduced and may not return to normal for several days. Yet, in the interim, the circulation may function quite adequately. Obviously, the vascular bed is able to adjust itself to an abnormal blood volume, and also a balance between capillary pressure and colloidal osmotic pressure may occur at abnormal levels. Ultimately the normal condition is restored, with a normal plasma volume and a normal concentration of protein. The exact mechanism of this return to the normal state, with the regulation of the quantity of plasma proteins, as well as their concentration, that such a return implies, remains obscure.

A third axiom, which we also owe to Starling, is the law of the heart, namely, that the force of its contraction varies with the degree of diastolic filling. He utilized this law and his hypothesis of fluid balance to explain not only the venous engorgement of cardiac failure, but also the increase in blood volume that accompanies it. He visualized then (1909) a regulation so arranged that, although the blood volume would normally vary rapidly through a small range, it might under abnormal conditions show considerable and lasting changes.

There appear, therefore, to be two conditions under which blood volume varies, namely (1), a primary change in the blood to which the size of the vascular bed is adjusted, and (2) a primary change in the vascular bed to which the blood volume is adjusted.

Turning from these axiomatic principles to a consideration of established clinical conditions, let us try to group such clinical states into these two types. Primary changes in blood volume include reductions caused by hemorrhage,[5] dehydration (including that secondary to artificial pyrexia),[6] surgical shock,[7] and anemia.[8, 9] Primary increases in blood volume include the plethoric conditions which are generated by venous infusion or blood transfusion,[1, 10] and probably polycythemia vera.[9] Primary changes in the vascular bed which lead to increases in blood volume occur with symptomatic polycythemia, cardiac disease, congestive heart failure,[11] and hyperthyroidism.[12] Primary decreases in the vascular bed which lead to similar changes in blood volume are less well known, but one such condition is myxedema.[12]

The changes in blood volume in these clinical conditions may be very large. Reductions of blood volume caused by dehydration can amount to 18 per cent; increases in blood volume with congestive heart failure, according to Gibson and Evans,[11] average 40 per cent, and may attain 141 per cent. Similar increases may occur in polycythemia vera.[9] In contrast with these enormous variations, temporary alterations in blood volume produced by acute changes in environmental temperature,[13] eating, change of posture, and the like, appear rarely to exceed 10 to 15

per cent. They might, therefore, be regarded as of no clinical importance. Such a deduction would be unwarranted. The proverb that it is the last straw that breaks the camel's back is peculiarly applicable to medicine. The contrast between the effects of mild exercise on the normal subject and on the seriously ill patient exemplifies this. Such minor adjustments may, therefore, be important in upsetting balances which are temporarily in a precarious situation.

If subjects be exposed continuously to environmental temperatures near the extremes which are tolerable without either hyperpyrexia or violent shivering, much larger changes in blood volume may develop. In my laboratory,[14-16] changes have been observed which sometimes appear to exceed 20, or even 40, per cent. I propose to describe some of these, for I believe that these changes, and those in the cardiovascular system that accompany them, are concerned with climatic effects on the incidence of cardiovascular disease. Petersen[17] has performed a service to medicine in redirecting attention to the marked effect of climate on disease. His statistical data are convincing, however much one may differ with his analysis. May I draw your attention to a single one of his curves. This relates to the incidence of cerebral hemorrhage in Chicago, in 1932. The incidence was minimal in the warm months of the summer, and maximal in the spring. There was a sharp increase in the incidence in the early cool weather of the fall.

A similar effect of rapidly changing temperatures was demonstrated by the number of monthly admissions of hypertensive patients with circulatory failure in Philadelphia, as analyzed by Dr. L. B. Laplace.[18] You may well criticize the unwarranted implication that these seasonal effects are in any way correlated with alterations in blood volume. Admittedly, this implication is pure conjecture. The seasonal exacerbations might depend on the respiratory infections which are common in the spring and fall. However, some evidence, although it is very indirect, may be adduced to show that seasonal changes in blood volume are concerned. Changes in blood volume are likely to be associated with changes in plasma protein concentration. Data in the literature[19] give some indication that there are seasonal variations in this protein concentration, although I have been unable to find any statistical study on man. Such a study, however, has recently been made on horses by Dr. A. H. Craige and Dr. J. D. Gadd,[20*] of the Veterinary School of the University of Pennsylvania. They have kindly allowed me to reproduce the unpublished curve of their results, which is shown in Fig. 1, for comparison with an inverted curve of the incidence of circulatory failure in hypertensive subjects (Dr. L. B. Laplace's data). There is an obvious similarity between the two curves, although they relate to different species (both sweating animals), different localities, and different years. The data suggest that the climatic changes which induce circulatory

*To appear soon in the American Journal of Veterinary Science.

failure in patients with cardiovascular disease also induce, in horses, changes which are likely to be associated with altered blood volumes.

In considering problems dealing with blood volume, it is necessary, first, to turn our attention to the relative importance of different sections of the vascular bed in accommodating the blood. My predecessor in this lectureship, Dr. C. K. Drinker, drew your attention to the careful analysis of the vessels of the dog's stomach which was made by Mall. I, in my turn, wish to draw your attention to the quantitative study of the vascular bed in the intestine of the dog, also made by Mall, and analyzed by Schleier.[21] Mall ascertained the diameter and number of the various branches of the mesenteric artery. From these data I have calculated the volume of blood contained in the various segments of this system. The figures are given in Table I. It will be seen that 73 per cent of the blood in the splanchnic system can be contained in the venules and veins, and 46 per cent in the larger veins themselves. The importance of the muscular coat of the veins thus becomes clearer, for it must be able to modify the reservoir function of these vessels. Whether the same proportional capacities exist in other parts of the vascular bed is uncertain, but even superficial examination demonstrates that a large amount of blood may be contained in the venous system.

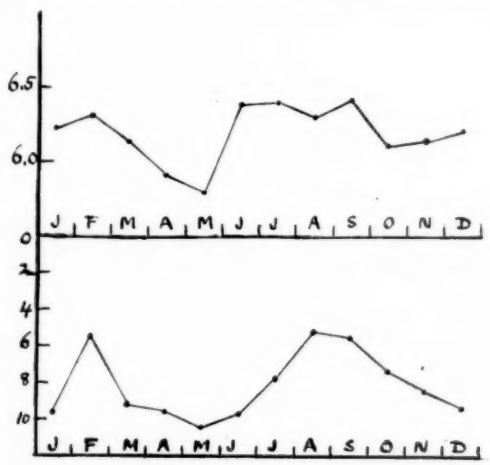

Fig. 1.—The monthly average plasma protein concentrations (Gm. per 100 ml.) in horses (data of Craige and Gadd) are plotted above, and the number of monthly admissions of hypertensive patients with cardiovascular failure to the Philadelphia General Hospital in another year (Laplace's data) below. The latter curve is plotted inverted.

The importance of veins as blood reservoirs was recognized by Starling, as well as the necessity of having an adequate pressure in the venous system in order to obtain adequate filling of the heart. Bearing in mind his principles, we may re-examine the more exact data which are now available, in order to ascertain the type of control involved. We may select experimental plethora, hemorrhage, and dehydration during pyrexia as examples of the effects of *primary changes in blood volume,*

TABLE I

MESENTERIC BLOOD VESSELS IN DOGS (OF 6 TO 7 KG. WEIGHT) CALCULATED FROM MALL'S DATA, AS ANALYZED BY SCHLEIER

TYPE			NUMBER	DIAMETER (CM.)	VOLUME OF CONTENTS (ML.)	TOTAL VOLUME (ML.)
a	Larger arteries	Mesenteric artery	1	0.30	0.42	
		Main branches	15	0.10	0.54	
		End branches	45	0.06	0.51	1.47 (8.7% of whole)
b	Smaller arteries	Intestinal branches	1,899	0.014	0.28	
		Last branches	26,640	0.005	0.63	
		Branches to villi	328,500	0.0031	0.37	
		Arteries of villi	1,051,000	0.0024	0.84	2.12 (12.6% of whole)
						Total all arteries 3.59 (21.3%
c	Capillaries	Capillaries of villi	47,300,000	0.0008	0.95	Total of capillaries, 0.95 (5.6% of whole)
d	Venules	Veins at base of villi	2,102,400	0.0026	1.16	1.16 (6.9% of whole)
e	Small veins	Veins before submucosa	131,400	0.0075	0.58	
		Last branches submucosa	18,000	0.013	0.36	
		Last branches intestinal	28,800	0.0064	1.23	
		Intestinal veins	1,899	0.028	1.19	3.36 (19.9% of whole)
f	Larger veins	Last branches mesenteric	45	0.15	3.09	
		Branches mesenteric	15	0.24	3.01	
		Mesenteric vein	1	0.30	1.68	7.78 (46.3% of whole)
						Total all veins and venules, 12.30 (73.1% of whole)

and the large increase that accompanies cardiac failure as an example of *primary change in the vascular bed.* Three of these were carefully analyzed by Starling. We may then examine the probable effects of seasonal changes in blood volume.

A primary increase in blood volume produced by the injection of defibrinated blood into a dog was carefully studied by Starling. His classical description may be followed, for little can be added to it. Although transfusions in man involve the same principles, they are not normally given rapidly enough, or in sufficient quantity, to produce any marked changes.[10] Starling[1] described his experiments as follows: "The injection increases the filling of the heart. . . . On this account the arterial pressure rises. A rise in arterial pressure brings about a reflex dilatation of the arterioles and therefore a difference in the distribution of pressure within the vascular system. The venous pressure rises and the

greater quantity of the injected fluid is accommodated in the big veins. There is, as the result of the rise of capillary pressures, an increased leakage of the fluid constituents of blood plasma. Evidence of this leakage is afforded by an examination of the blood a quarter of an hour after the injection. The haemoglobin content is found to have largely increased, showing that the greater part of the fluid of the defibrinated blood has already escaped out of the vascular system, leaving behind the blood corpuscles and a certain proportion of the proteins of the plasma. . . . The concentration of the blood raises the viscosity of this fluid and therefore the resistance to its flow through the capillaries. If the injection be very large, the resistance may prove too much for the heart; the systolic volume of this organ becomes larger and larger, so that more blood accumulates behind it in the big veins. . . . Finally, the overdilated heart is unable to effect any onward movement of the blood at all, and the animal dies. Bleeding the animal brings about a rapid restoration of the heart's functions.'' Therefore, he thought that the increased volume is partly reduced by filtration into the tissues, but is accommodated mainly by an increased capacity of the vascular bed, caused by dilatation, active or passive, of arterioles and veins. The increased volume may cause a rise in blood pressure.

The compensating factors which counteract a reduction of blood volume caused by hemorrhage involve the opposite reactions of constriction of the arterioles and veins. They are well demonstrated by the data of Meek and Eyster.[22] Figs. 2 and 3 present some of their data, replotted. The results obtained on an unanesthetized dog are shown in Fig. 2, and, on an etherized dog, in Fig. 3. The capacity to adapt is much lowered by ether. Under ether, a loss of 8 Gm. per kilogram of body weight produced profound effects which even 28 Gm. per kilogram failed to induce in an unanesthetized animal. The anesthetic presumably depressed reflex control, besides affecting the permeability of vascular membranes. In both anesthetized and unanesthetized animals, small, rapid hemorrhages (amounting in unanesthetized dogs to 2.1 per cent of the body weight) resulted in little or no change in pulse rate or cardiac output. Adjustment appeared to be attained partly by a partial recovery of normal blood volume by the absorption of fluid, and partly by reduction of the vascular bed through constriction. Hemorrhages of intermediate size (20 to 30 per cent of the body weight in the unanesthetized dog) still produced little change in pulse rate and only a slight reduction in venous pressure and cardiac output; the arterial pressure was actually raised, and marked constriction of superficial capillaries and venules was noted. Measurements of hemoglobin concentration indicated that the replacement of blood loss by fluid absorption was slight. Carotid sinus regulation of pressure levels is inadequate to explain the *rise* in arterial pressure. In the earlier stages, vasoconstriction, so induced, or brought about by inadequate venous filling (McDowall reflex), is able to maintain both circulation rate and blood pres-

sure levels close to their normal values; in these earlier stages, contraction of large veins is probably an important factor. In this later, more critical stage of repeated hemorrhage, the rise of arterial pressure appears to be the result of a last desperate effort to maintain an adequate venous return. It probably depends on marked constriction of arterioles, not for its value in increasing resistance, but in order that the blood so liberated may be utilized to maintain venous distention.

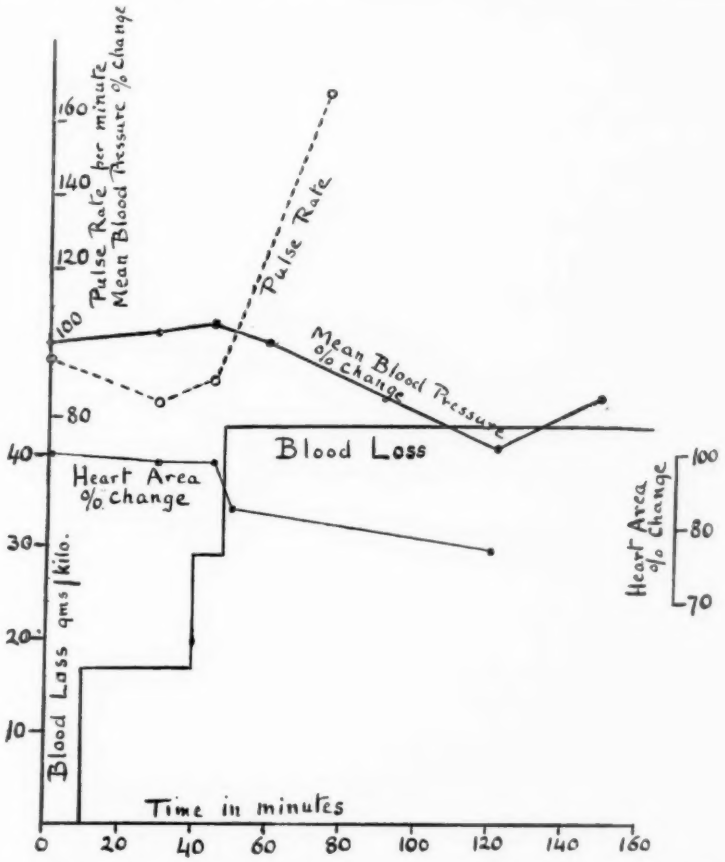

Fig. 2.—Plot representing data from a hemorrhage experiment on an unanesthetized dog (Meek and Eyster, experiment 10). The percentage change in mean blood pressure, absolute level of pulse rate, percentage change in the area of the heart's shadow, as ascertained roentgenologically, and the blood loss in grams per kilogram of body weight are shown as ordinates, with time, in minutes, as abscissae.

This would mean that arteriolar control was being used for its reservoir effect. It may, perhaps, be induced through a depressed circulation to receptors of the carotid body type, or from receptors affected by lack of distention in the veins. A decrease in blood volume may cause a rise in blood pressure.

In favor of the idea that such a constriction of arterioles may have a reservoir effect are the data obtained during pyrexia and dehydration.

Fig. 4 represents an experiment on my collaborator, Dr. J. C. Scott.[23] Dehydration amounting to 3.1 per cent of his body weight induced symptoms comparable with those of the critical stage of hemorrhage, for the reduction in blood volume was combined with a vascular dilatation in the skin resulting from the pyrexial conditions. The pulse rate was mounting rapidly, and this change was associated with an increase in arterial pressure. Cardiac filling was inadequate, for the basal stroke volume of 71.5 c.c. had been reduced to 38.5 c.c. The cardiac output

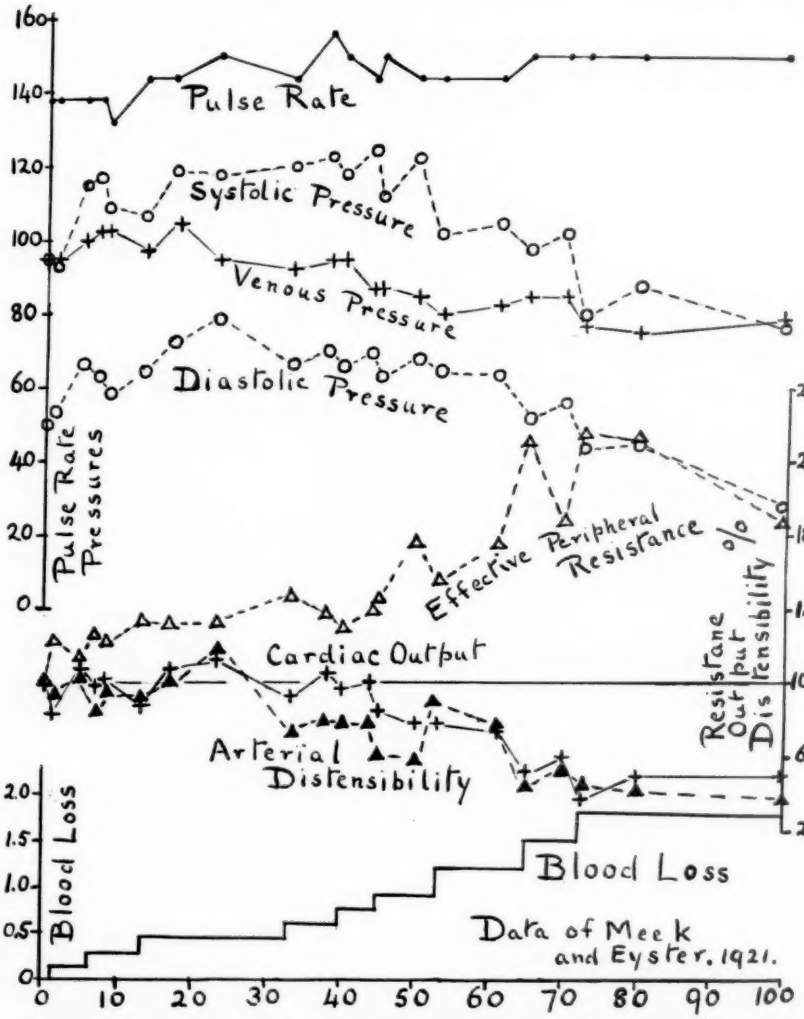

Fig. 3.—Plot representing data from a hemorrhage experiment on an etherized dog (Meek and Eyster, experiment 7). Pulse rate, systolic and diastolic pressures (in mm. Hg), and venous pressure (in mm. of water) are shown above as ordinates, with time, in minutes, as abscissae. The lowest graph shows the blood loss in grams per kilogram of body weight. In the intermediate curves the percentage changes in cardiac output per minute (crosses), the effective peripheral resistance (open triangles), and arterial distensibility (solid triangles) are shown. The resistance was estimated from the ratio of mean pressure to cardiac output, and the distensibility from that of pulse pressure to stroke volume. Evidence of constriction of both large arteries and arterioles accompanies the initial rise in arterial pressure.

was normal for basal conditions, but very subnormal for such a pyrexial condition. The subject felt extreme prostration, and showed the reflex restlessness that accompanies inadequate venous return (as after hemorrhage). Analysis showed that there was a quite marked increase in the average arteriolar constriction (increased effective peripheral resistance), despite the vasodilatation in the skin. Here again, therefore, the commencing failure of venous return was combatted, not only by muscular movements which would act as a pump, but also by pronounced

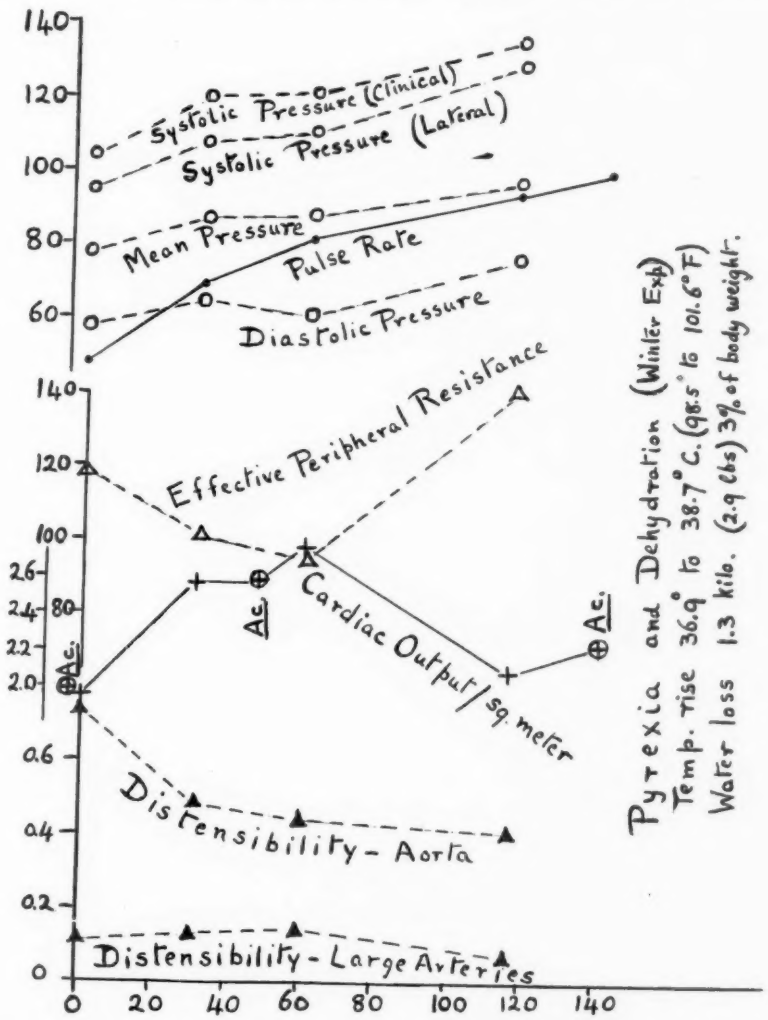

Fig. 4.—Data from a pyrexial experiment, with dehydration, in man (hot bath). The estimates of systolic, mean, and diastolic pressures (mm. Hg), of pulse rate, calculated effective peripheral resistance, cardiac output per minute per square meter of body surface, and distensibility of the aorta and of other large arteries are shown as ordinates from above downward, with time, in minutes, as abscissae. Cardiac output was estimated by the acetylene method (*Ac.*), or from pulse pressure and distensibility. The distensibilities were estimated from pulse wave velocities, and are expressed as probable increases in volume in milliliters per square meter of body surface per millimeter of mercury increase in pressure.

arteriolar constriction in areas other than the skin. The rise in arterial pressure appeared to be an index of considerable strain on the system.

It is also well established that a variation of blood volume may be produced secondarily by a primary change in the vascular bed. A simple experimental example is the increase in blood volume which results from the reduction of vascular tone caused by sympathectomy, as described by Dr. W. B. Cannon in the first of these lectures.[24] The enlargement of blood volume in hyperthyroidism is presumably also dependent on the general, persistent vasodilatation in both the muscles and the skin that must accompany the high metabolic rate. It is illogical to expect the organism to provide the necessary blood by persistent vasoconstriction in other areas. The mechanisms of control would presumably be the same as those involved in regeneration of blood following hemorrhage. The great increase in blood volume which is associated with cardiac decompensation is probably also secondary to the vascular conditions. It is so important that it deserves detailed attention. Probably Starling's hypothesis is at least partly correct, for he predicted that this increase in volume must develop, even before it was actually demonstrated by Lorrain Smith and McKisack,[25] in 1902.

Starling[1] described the origin as follows: "Any failure of the pump ought to tend to equalisation of pressure on the two sides of the system, i.e., to a fall of arterial and a rise of venous pressure. . . . Why is it that in cases of heart disease we find a normal arterial pressure? . . . The maintenance of an adequate output involves a continuance of high venous pressure, which can only be secured simultaneously with the maintenance of a normal arterial pressure by universal vasoconstriction. The condition, indeed, is analogous in the arteries and capillaries to that produced by bleeding, although in the case of heart failure the vascular system is bled into the veins. . . . Lowering of capillary pressure causes increased absorption. . . . The total volume of circulating fluid must be increased. . . . Chronic cyanosis must have the same effect as chronic exposure to an atmosphere of low oxygen tension, a direct excitation of the function of the bone marrow. As a result, a condition of real plethora is set up; and the vascular system contains an excess of blood of normal concentration and composition."

Modern work has amply confirmed Starling's prediction; the increase in blood volume can be very large.[11] The increase of cell volume somewhat exceeds that of the plasma,[11, 25] but, for the most part, the composition is normal, as Starling predicted. Serum protein concentrations are normal.[26] Starling regarded the blood volume increase as a compensation, and compared the changes to the effect of a hemorrhage into the individual's own veins. The clinician will be struck, however, with the similarity between Starling's description of plethora and the condition of the failing heart. The obvious improvement in such cases after venesection is hard to explain as the result of a compensatory increase in blood volume. There remains, therefore, a dilemma.

The changes in blood volume that may be observed in subjects who are exposed to variations in climatic conditions are probably also secondary to changes in the vascular system. If cardiac failure is accompanied by large changes in blood volume, these effects of climate may be presumed either to add to, or to detract from, the load. They must, therefore, be considered on the same hypotheses.

An increase in blood volume on exposure of normal subjects to tropical conditions was first described by Barcroft, et al., in 1922.[27] We have found similar changes in subjects who were exposed to warm or cool room conditions continuously for periods of four to seven days.[14] It is not certain that they are permanent, but they last for days. A difficulty arises in that the changes we observe commonly exceed 20 per cent, and may be as great as 40 per cent; on the other hand, Dr. W. H. Forbes[28*] has only been able to find changes of a much smaller magnitude in subjects who were examined in Boston and Mississippi. I am indebted to him for permission to quote this personal communication. With this discrepancy in mind, Miss M. E. Maxfield, Dr. J. C. Scott, and I made measurements on four students over a period of two months in Philadelphia during the present spring. With the fairly sudden onset of spring weather, all showed an increase in blood volume. The increases averaged 19.9 per cent (maximum, 33.6 per cent; minimum, 8.9 per cent). There can be little doubt that a considerable increase in volume may occur in the spring, for a temporary fall in hematocrit reading, hemoglobin percentage, and concentration of serum protein was observed in all four subjects. The functional value of this change and the mechanisms by which it is probably brought about must, therefore, be considered. In considering these climatic effects and their probable relationship to cardiovascular disease, let us, in order to simplify the presentation, pass frankly into the borderland between fact and fancy. We can then attempt to formulate hypotheses to explain our observations. In so doing we must always remember that we are dealing partly with fancy. We must, therefore, set out to devise new observations to test our hypotheses further, and try to prevent the development of an unwarranted sense of security, a failing which has been of late so sadly prevalent in many fields.

In response to warmth there is a sequence of changes. Acute warmth produces an initial vasodilatation in the skin, with enlargement of the superficial veins, some dilution of the blood secondary to lowered capillary pressure, and a fall of blood pressure. If the warmth is near the limit for adaptation to acute changes, marked dilatation of skin vessels is possible only when a really extensive vasoconstriction in other areas makes blood available for the skin. The person has, in Starling's imagery, bled into his skin capillaries, venules, and large veins. The

*These data have recently been published: Forbes, W. H., Dill, D. B., and Hall, F. G.: The Effect of Climate Upon the Volumes of Blood and of Tissue Fluid in Man, Am. J. Physiol. 130: 739, 1940.

reduction in the size of the more central vascular bed which is thus rendered necessary implies constriction of the arterioles in the central organs for a reservoir effect, so that the blood pressure is increased as it is after a moderate hemorrhage. Lowered capillary pressure increases the absorption of fluid. The lowered concentration of plasma protein causes plasma protein formation. We may imagine some reversible process, probably in the liver, which generates protein until the normal concentration in the plasma is reached. In the vasoconstriction the blood vessels supplying the bone marrow are concerned, so that this tissue, deprived of a normal supply of oxygen, is stimulated to increased production of cells. This, however, proceeds much more slowly. Once the blood volume has been increased, the necessity for central arteriolar constriction is removed, and the blood pressure returns to normal.

In response to warmth there is, therefore, an initial reduction in both plasma protein and erythrocyte concentration, with a more rapid return to normal protein, than to normal cell, concentration. The full change in blood volume does not develop until the plasma proteins have been increased in quantity, nor does it reach its full effectiveness until the cells have been proportionately increased. Since slow adjustments in metabolism[15] may play a role in climatic adaptation, the demands for skin dilatation, and the increased blood volume thus made necessary, may ultimately be less than in intermediate stages. The cardiovascular adjustments during this process of adaptation are much modified by the blood changes. In the early stages circulatory efficiency is poor; the pulse rate accelerates unduly on standing, and poor venous return is responsible for a very small standing stroke volume. With increased blood volume, venous return is improved; the standing pulse rate is much slower and the stroke volume greater.[16] Whether these circulatory changes depend on those in blood volume is less certain. Under the controlled conditions of experiments in an air-conditioned room they seem to be related; with less well-controlled conditions, such as those already mentioned in connection with the experiments on students during the spring, such relationships have so far been indefinite. It seems necessary to have the increase in blood volume before increased circulation in the fingers or dilatation of superficial veins can be utilized to the full for the maintenance of heat balance.[16]

The sequence of adaptation to cold is the opposite. Acute cold produces constriction of the small vessels, and also of the large veins, of the skin, with an initial rise in blood pressure and loss of fluid from the blood. If the cold is near the limit for adaptation, full skin constriction necessitates the displacement of a large volume of blood to some other area, and therefore a marked dilatation of central vessels, including the arterioles, to obtain their reservoir effect. The blood pressure, therefore, falls. Even so, a complete, generalized constriction of the skin vessels and veins is not attainable, and several days may elapse before reduction in blood volume allows this to take place.[16] It appears that

the body often tries to conserve plasma proteins, so that, with fluid loss from the blood, the concentration of plasma proteins may rise considerably above normal. In some persons this change may not be marked or of long duration. In all subjects the erythrocytes tend to be conserved, so that there is some rise in the hematocrit reading, and also in hemoglobin concentration. These changes must result in an increase of blood viscosity. There is (consequently?) no immediate return to a normal blood pressure level; the lowered pressures are replaced by supernormal pressures.

The occurrence of these adaptations in sequence at different rates of development makes the whole process complex. For instance, warmth induces, first, a fall of blood pressure, then a rise, and then a fall to normal or subnormal levels; cold causes, first, a rise, then a fall to subnormal levels, and then a second supernormal period before a normal level is regained. It is readily possible that the effects of warmth and cold in sequence may be additive, instead of cancelling one another, as far as blood pressure is concerned. In fact, in the early cool weather of the autumn the blood pressure is likely to be higher than in much colder weather in the spring.[16] May I introduce the term *consecutive adjustments, or historically determined balances,* to indicate these roundabout methods of return to a normal state? The return to cool conditions following a period of warmth may be compared with the retirement of an army to defensive positions after an offence. The ground may be the same as that covered at some stage of the offence, but the position is very different. Thus, when persons are exposed, let us say, to an environmental temperature of 29° C. (84° F.), their condition depends on where they have been previously. If they have previously been adapted to cold, the blood volume is subnormal for vascular comfort, and plasma protein and erythrocyte concentrations are also subnormal. If, on the other hand, they have previously been adapted to heat, the blood volume is supernormal for comfort, plasma protein and erythrocyte concentrations are above normal, and the viscosity of the blood may be excessive.

Another factor which influences these adjustments is posture. It is well known that concentration of the blood accompanies the assumption of the erect position. Fluid is lost from the blood into the tissues, particularly in the dependent legs, with a resulting increase in the concentration of erythrocytes and plasma protein. It is not known whether the percentage change in blood volume caused by changes in posture does, or does not, vary with climatic conditions, but it is not improbable. We are certainly not justified in saying that observations made under basal conditions give us a picture of the average state of the subject, or of changes in his state.

We should not assume that either plasma protein or erythrocyte generation is likely to be uninfluenced by postural reactions, constancy of temperature conditions, and the like. In particular, night and day temperatures are likely to act somewhat differently. If new formation

of plasma proteins is continued until a certain concentration is reached, conditions at night, when the subject is lying down and blood concentrations are minimal, should be important. Such concentrations should be particularly low when the persistence of high temperatures prevents any constriction of skin vessels. There is some evidence that plasma proteins may be formed more rapidly than they are removed.[14] Some such sequence of events, with formation of plasma proteins particularly at night, might account for the higher concentrations of plasma protein in subjects who are exposed continuously to high temperatures,[14] as well as in horses during the hot summer months (Fig. 1). On the other hand, it is probable that there is, in addition, some more complex mechanism for regulation of the quantity of plasma protein, and, consequently, of plasma volume.

The increase in blood volume caused by warmth may, therefore, be regarded as very similar to that in cardiac failure. In the one case the person bleeds, as it were, into the superficial skin veins, and, in the other, into deeper, large veins. In the reaction to warmth the increase in volume is certainly a compensatory mechanism, and is accompanied by a slower pulse rate, a larger stroke volume when standing, and other evidence of greater cardiovascular fitness. There remains the dilemma that, in cardiac failure, bloodletting is so commonly of great benefit to the patient; the blood volume has apparently been too large. To explain this, one has only to assume that there is a constant reaction to chronic circulatory failure, in which peripheral vasoconstriction and increased erythrocyte formation, together, bring about greater venous filling, with stretching of the heart muscle in diastole. This reaction would then proceed to raise the venous pressure when cardiac output decreased, regardless of whether the venous pressure was rising towards its optimum value or had already passed it.

Reactions to temperature and posture with modifications of blood volume would then play their part. Heart failure would most commonly develop when the patient was doing light work in the erect posture. Adaptation to this work might already have been attempted by utilization of the venous engorgement mechanism to or beyond its optimum. When failure occurs, and the patient is forced into a position of partial recumbency, the blood volume is still further increased by the fall in capillary pressure in the dependent parts of the body and the consequent absorption of excess tissue fluid. Venous engorgement is thus exaggerated. This exaggeration in the recumbent position may be one of the many factors that make complete recumbency impossible for the patient with heart failure. If this series of events is complicated by a sudden change from warm to cooler weather, necessitating shunting of the skin blood to the deeper vessels, adverse conditions may be aggravated. Even in normal subjects, a change from hot to cooler weather may be associated with evidence of vascular engorgement, such as epistaxis. The abrupt changes of temperature utilized in our experi-

mental room have not given rise to symptoms in the young subjects that have been mostly employed. Symptoms might be more in evidence in older subjects. In the one older subject whom we used (who is somewhat hypotensive), the only symptoms during abrupt warming were edema of the feet, weakness, and incapacity for mental concentration, and, during abrupt cooling, palpitation on going to bed.

Abrupt changes in temperature might affect the circulation in many ways. A sudden change to warmer weather might leave the blood volume too low, and cause inadequate filling of a heart which needed a high venous pressure for effective action. Vasoconstriction, with a rise in arterial pressure and an increased load on the heart, might result. A sudden fall in temperature might make the blood volume excessive in conditions characterized by superficial vasoconstriction, and so cause venous engorgement. This seems to be a sequence which is likely to give rise to a vicious circle. High blood pressure might develop either on exposure to warmth, with an inadequate venous return, or, in the initial reaction to exposure to cold, with a relative plethora, and either might play a part in facilitating cerebral hemorrhage. Again, the low pressures that develop in the second stage of exposure to cold might be accompanied by poor coronary supply and favor coronary thrombosis. In any case, all of these reactions are likely to be not only of greater importance, but also of greater magnitude, when the cardiovascular system has been rendered inelastic by disease or old age. Increased viscosity may be of little importance in normal vessels, the lumens of which can be adjusted. It may be of immense importance in diseased vessels with small and unadjustable lumens. Clinical observation of such subjects during periods of rapidly changing temperature might do much to clarify the situation. One important factor which determines plasma volume is the quantity of plasma protein in circulation. It is, consequently, a pity that in many reports of plasma volume measurements no data are given concerning plasma or serum protein concentration.

Lastly, we have supposed that there is a constant reaction to chronic circulatory failure, in which venous engorgement plays an important role; how are we to explain its absence in some cases? As Starling stated in the passages quoted, the failure of the pump mechanism causes a rise in venous pressure, and this is true whatever the condition. However, the real picture of massive venous engorgement requires a considerable increase in blood volume, with its concomitant increase in the circulating plasma protein and erythrocytes, and these processes take time to develop. It is true that a very similar venous engorgement may develop acutely, without such an enlarged blood volume, but only by generalized arterial constriction in acute reactions that cannot be long maintained. Failure without venous engorgement can, therefore, take place when the changes are too rapid to allow the compensatory increases in blood volume to occur, and when the effects of intense vasoconstriction

are prevented by toxemia, vasomotor fatigue, increased permeability of the capillaries in shock, and the like.

Many other points should have been discussed. It is probable that some cardiovascular disabilities result from a disordered control of blood volume. Some cases of postural hypotension may belong in this class. More suitable methods for blood volume measurement are required, although this is not the time and place for a discussion of technique. I believe, however, that recent modifications of the carbon monoxide method may make it more suitable for clinical use than the dye methods, with their demand for numerous blood samples.

In conclusion, I do not feel that I need apologize for my extensive references to, and quotations from, that grand old master of physiology, Professor Starling. I can only regret that he is not still alive to analyze these newer data with the consummate skill which he used for the older, and that I myself have not been in the audience listening to him.

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ROENTGENOLOGIC STUDIES OF THE SIZE OF THE HEART IN CHILDHOOD

I. Three Different Types of Teleroentgenographic Changes Which Occur in Acute Rheumatic Fever

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INTRODUCTION

IN A PREVIOUS paper,[1] evidence was adduced to show that in rheumatic heart disease the size of the heart depends not primarily upon the severity of the valvular lesion, but upon the extent of the myocardial damage. The author cited one case in which the heart appeared to be within normal limits four years after the development of mitral and aortic insufficiency and stenosis. In two other cases, notwithstanding valvular damage, the size of the heart had remained stationary over a period of years. Finally, there was the case of a child whose heart had been enormous at the age of 5 years, but seven years later was within normal limits. In the latter case, superimposition of the teleroentgenograms which had been taken at yearly intervals showed that the change in the size of the heart was a relative one, i.e., the heart had remained constant in size and the chest had grown.

How great is the significance of these observations depends upon a number of factors, such as the centering and target-film distance, the phase of the cardiac cycle, and the phase of respiration. Each of these factors is subject to minor variations. Nevertheless, when six successive roentgenograms, taken at yearly intervals, show that the heart is always of the same size and contour, it is improbable that this uniformity is the result of a summation of chance variations. Certainly chance cannot be a factor if similar findings occur in a number of different cases.

In the paper just referred to, the cases were cited as examples of phenomena which have been observed in acute rheumatic fever. The purpose of the present investigation was to study the changes in the size of the heart, as ascertained by means of teleroentgenograms, in a large series of cases of rheumatic heart disease. As a result of the study, we have been able to differentiate three definite and distinct sequences of changes in the size of the heart. In one group of cases, in spite of valvular lesions, the size of the heart remained within normal limits, and its increase in size was that of normal growth; in the second group

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of cases the heart, after it enlarged, remained stationary in size while the chest grew; in the third group there was progressive cardiac enlargement. The purpose of this paper is to present these observations and to compare briefly the clinical course of the disease in the several groups.

MATERIAL AND METHOD

The study is based upon routine teleroentgenograms, taken on patients who were being cared for in the cardiac clinic. Inevitably, in many instances, we failed to obtain teleroentgenograms as frequently as, in retrospect, would have been desirable. Further, not all of the roentgenograms were satisfactory. In some the patient was rotated; in others the exposure was made at the end of extreme inspiration or expiration. A few were open to question because of doubt concerning the target-film distance. All such roentgenograms were discarded.

Changes in the size of the cardiac shadow caused by pericardial effusion were not included. In every case in which this was suspected, teleroentgenograms suggestive of effusion were excluded. We, of course, included not only the cases of chronic valvular disease, but also those of acute myocarditis.

Our method of study was similar to that used by Palmer,[2] namely, the changes in the size of the heart were studied by the superimposition of one teleroentgenogram upon another. Palmer's studies were made on adults; he considered that changes in the size of the heart were significant only if the size of the chest remained constant. Inasmuch as we studied children, such criteria were not possible; it was essential to take into consideration the factor of growth.

The cardiothoracic ratio offers the simplest means of comparing the rate of growth of the heart and the chest. We appreciate fully that this method is not an exact one; nevertheless, speaking in broad terms, it does give an indication of the relative size of the heart and chest.

In addition, we attempted to compare the size of the heart with the theoretically normal size for persons of the same age, height, and weight. This method, too, is not accurate, for none of the studies on normal subjects include persons from 5 to 20 years of age.

For children between the ages of 4 and 16 years, we used the standards established by Ziskin.[3] He correlated the transverse diameters of the heart and the chest with height and age. Whenever possible, we correlated the size of the heart with height. In the few instances in which the height was not recorded, we had to correlate the size of the heart with the age* of the child. For children over 16 years of age we used the normal standards of Ungerleider and Clark.[4]

Ungerleider and Clark's standards start with the age of 15 years, a weight of 83 pounds, and a height of 60 inches. These investigators believe that after the age of 15 years the size of the heart varies not with age, but with height and weight. The majority of children reach 60 inches in height and 83 pounds in weight in early adolescence. Therefore, in all instances in which our children had attained this height and weight, we used both standards, i.e., those of Ziskin and those of Ungerleider and Clark.†

*In such cases we also compared the transverse diameter of the chest with the normal for the age, in order to ascertain whether or not the child was of normal size for his age.

†Our group of supposedly normal subjects, i.e., those with a normal cardiothoracic ratio who were of average height and weight for their age, fell within the limits of normal for both sets of standards. There were seventeen children whose growth we had classified as normal who were over 60 inches in height and weighed more than 83 pounds. A comparison between the size of the heart in these cases with that given by Ungerleider and Clark showed that fifteen of the seventeen subjects fell within 5 per cent of the average for the height and weight; the remaining two were within 10 per cent of the average. The latter percentage of variation is at the present time regarded by Ungerleider and Clark as representative of the (continued on next page)

Our studies were based on frontal planes. We have no series of measurements in the oblique or lateral views and, therefore, can make no comparative studies of enlargement in the posterior plane. Great enlargement in the posterior plane usually alters the size or contour of the heart in the frontal plane. Although this is not always true, it is admittedly a source of error. It must also be admitted that these studies make no allowance for the volume of the heart or the thickness of the muscle wall. Granted these limitations, it is generally accepted that teleroentgenograms do give useful information concerning the size of the heart.

We did not attempt specifically to measure cardiac areas, because the method of superimposition of teleroentgenograms reveals changes in cardiac area. In a few instances, although the transverse diameter of the heart did not increase, the contour of the heart changed and the tracings clearly showed a definite increase in the cardiac area. Such cases* were not included in this study.

CASES IN WHICH THE HEART SHOWED NORMAL GROWTH

It is well known that there are many children who suffer from a single attack of acute rheumatic fever, and yet, in later life, show no cardiac abnormality. In addition, there are a few who suffer from multiple attacks of acute rheumatic fever without developing valvular heart disease. Some of these children never show any clinical evidence of cardiac involvement; others, during the acute stage of the disease, present slight, but definite, evidence of myocardial strain which disappears with the subsidence of the acute infection. The majority of these children do well. Their hearts remain normal. As the child grows, the heart increases in size in the normal manner. This phenomenon is familiar to all and calls for no comment. A case of this kind is presented merely to serve as a basis for comparison with those which follow.

CASE 1.—A. M. (H.L.H. No. 77466), a white girl, had had two comparatively mild attacks of rheumatic polyarthritis, each followed by chorea—the first in April, 1932, and the second in September, 1934. Throughout both attacks the child was kept at rest in bed. Each time, at the height of the rheumatic infection, although there was no demonstrable cardiac enlargement, examination of the heart revealed a soft systolic murmur which was transmitted to the axilla. After the subsidence of the rheumatic infection, all signs of cardiac strain disappeared and the girl has remained well.

The composite picture of the tracings of the teleroentgenograms is shown in Fig. 1. The various measurements are given in Table I.

*One case (Fig. 6*b*) is presented merely to illustrate the ease with which such cases can be differentiated from those with which we are concerned.

(continued from preceding page) limits of normal. Therefore, we concluded that for children of average height and weight the two standards were equally reliable.

There was a wide discrepancy between these two sets of standards when they were applied to obese children. This discrepancy is, in all probability, caused by the fact that Ungerleider and Clark included in their series a large number of short, stocky, heavily built adults and allowed for an increase in the size of the heart in proportion to the weight of the subject, whereas Ziskin studied subjects under 16 years of age and made no allowance for increasing weight. We believe that, in such cases, the normal size of the heart is probably represented by a value intermediate between the two standards.

The standards of Ungerleider and Clark were also inadequate when they were applied to patients who, because of illness, had lost weight rapidly. In such cases it is not to be expected that the heart will decrease in size in proportion to the loss of body weight. Therefore, it is clear that these standards cannot be considered precise. Indeed, all comparisons between the actual size of the heart and the normal for the age, height, and weight are but rough indices. Nevertheless, broadly speaking, we believe that they are useful indices.

TABLE I

DATE	AGE (YR.)	HEART T.D. (CM.)	CHEST I.D. (CM.)	C/T	HEIGHT (IN.)	WEIGHT (LB.)	AV. T.D. OF HEART (CM.)	PER CENT DEVIATION FROM AV.
May, 1932	8	8.7	18.3	47.5			8.9	-3
January, 1934	10	9.6	20.0	48.0	53	70½	9.5	0
January, 1935	11	10.0	21.5	46.5	56	72½	9.65	+4
November, 1937	13	10.2	23.7	43.0	61	92½	10.5	-3

T.D., Transverse diameter; I.D., internal diameter.

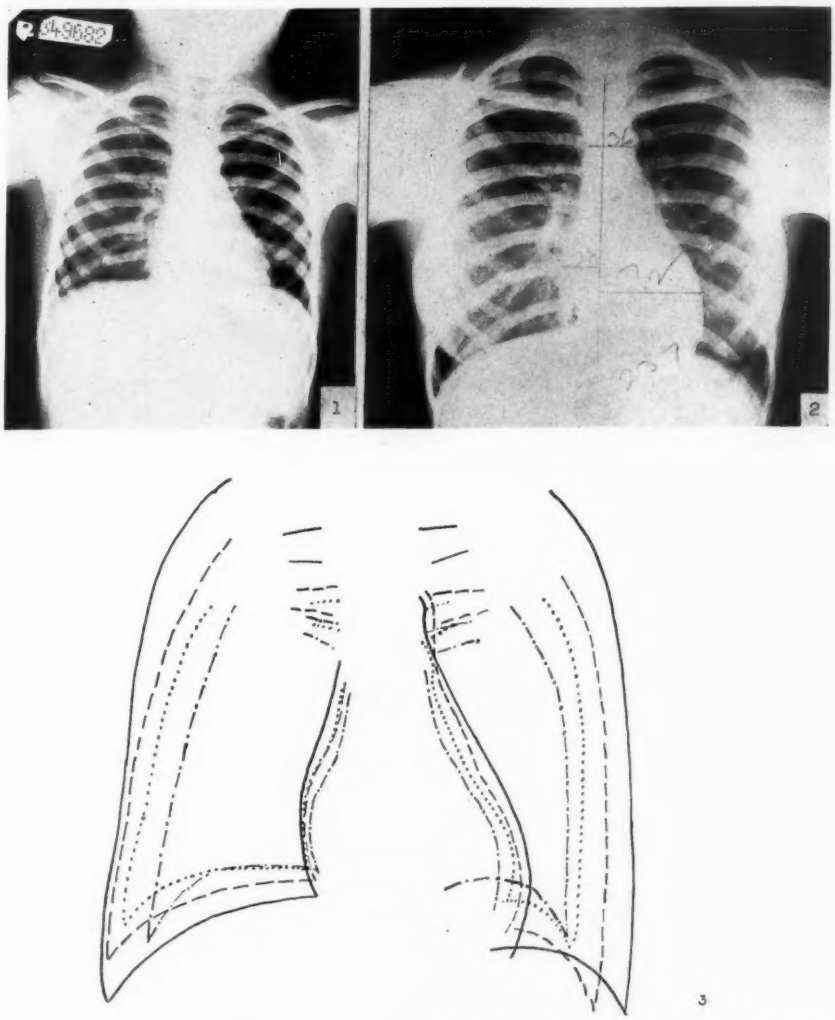


Fig. 1.—Normal growth. Case 1 (normal heart). *1*, Teleroentgenogram 5/4/32. *2*, Teleroentgenogram 11/10/37. *3*, Tracings of teleroentgenograms 5/4/32 — . — . —, 1/20/34 . . . . . , 1/14/35 — — — — —, 11/10/37 ————.

In this case, the transverse diameter of the heart increased steadily in proportion to the growth of the chest. The cardiothoracic ratio remained relatively constant until puberty, and then decreased, as it normally does. A comparison between the actual size of the heart and the theoretical average transverse diameter for her age, height, and weight also showed that the size of the heart closely approximated the normal. In this case it was only during the attacks of rheumatic fever that there was any evidence of cardiac involvement. The heart was never enlarged, and there was no evidence of chronic valvular damage. Hence, it is not remarkable that the growth of the heart was normal.

It is, however, highly significant that the same phenomenon can occur in cases of chronic rheumatic valvular disease, as illustrated in Case 2, in which the boy had an aortic insufficiency of seven years' duration.

CASE 2.—J. G. (H.L.H. No. 26003), a negro, was born in 1920. He was first seen at the Harriet Lane Home in May, 1930, at which time he had acute arthritis. Shortly after the onset of the illness he developed signs of aortic insufficiency. He was kept in bed for eight months. In May, 1932, he had a mild recurrence of polyarthritis, associated with fatigue and dyspnea. He had another mild recurrence of acute rheumatic fever in February, 1935. Since then he has remained well. The signs of aortic insufficiency have persisted.

The composite picture of the tracings of the teleroentgenograms is shown in Fig. 2. The actual measurements of the transverse diameter of the heart and chest are given in Table II.

In this case the cardiothoracic ratio was never above 43 per cent. It is evident that the size of the heart was always within normal limits, and that the increase in its size was proportional to the growth of the chest. This case clearly illustrates that aortic insufficiency does not necessarily cause the heart to enlarge out of proportion to the normal growth of the body.

In brief, we have observed forty-four children whose hearts have never been above the upper limit of normal size in spite of the fact that they have had acute rheumatic fever. In these children the increase in the size of the heart has been essentially that of normal growth. Of these children, thirty are similar to the first patient cited. They had mild infections. In fifteen instances the outstanding rheumatic manifestation was chorea. Some suffered recurrences; two had repeated recurrences. One child had eight, and another nine, attacks of chorea. All of these children at some time showed slight evidence of cardiac involvement; none has any residual evidence of valvular damage.

There are, however, fourteen cases which are similar to the second example in that the cardiac murmurs have persisted to date; nine have mitral insufficiency; three have aortic insufficiency; and one has mitral insufficiency and a mid-diastolic murmur. During the period of observation five of these children had recurrences of acute rheumatic fever; all of them were treated with long periods of rest in bed.

TABLE II

DATE	AGE (YR.)	HEART T.D. (CM.)	CHEST I.D. (CM.)	C/T	HEIGHT (IN.)	WEIGHT (LB.)	AV. T.D. OF HEART (CM.)	PER CENT DEVIATION FROM AV.
October, 1930	10	9.2	21.5	42.8	55	62½	9.6	-4
March, 1932	12	9.5	22.6	42.0	59	73½	9.9	-3
November, 1934	14	10.3	24.8	41.5	64	99½	*10.6*	*-2*
February, 1936	16	10.9	26.5	41.1	67	116½	*11.2*	*-2*
January, 1938	18	10.8	27.5	39.2	68½	128½	*11.7*	*-7*

T.D., Transverse diameter; I.D., internal diameter.
Italicized figures are those given by the insurance company.

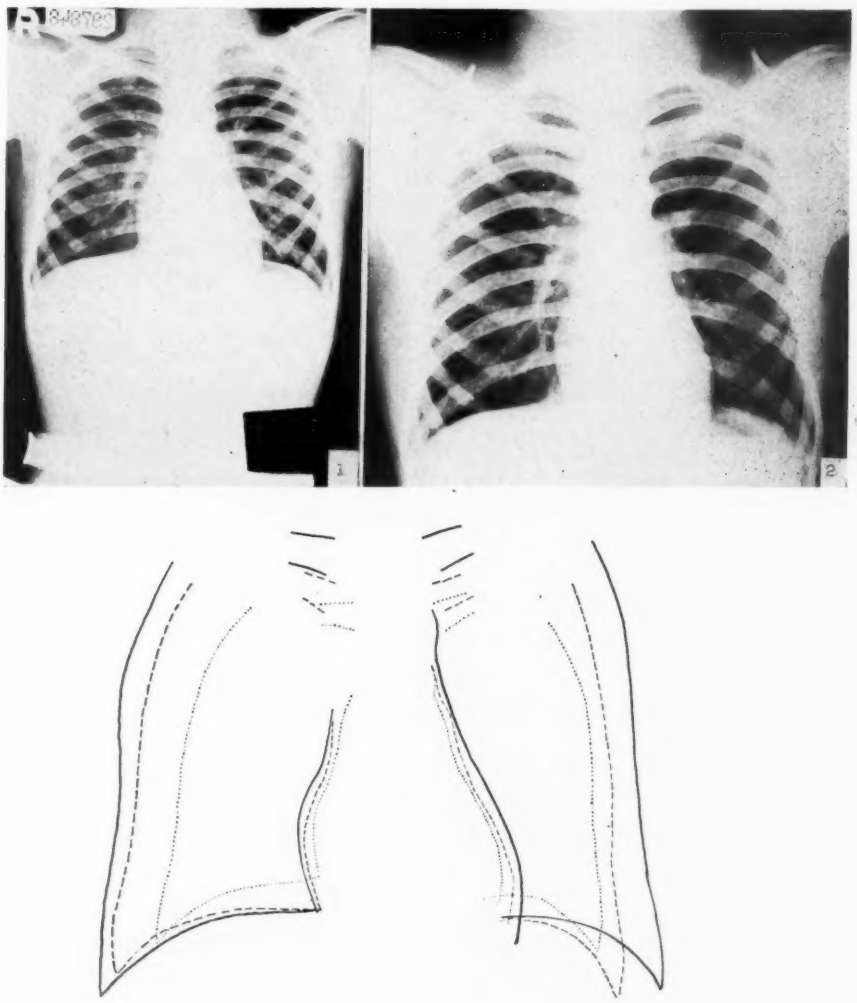


Fig. 2.—Normal growth. Case 2 (aortic insufficiency). *1*, Teleroentgenogram 10/13/30. *2*, Teleroentgenogram 1/27/38. *3*, Tracings of teleroentgenograms 10/13/30 . . . . . , 11/12/34 — — — — —, 1/27/38 ————.

The mortality rate in this group was low. Indeed, there was only one death. That patient had her first attack of acute rheumatic fever, accompanied by signs of mitral insufficiency, at the age of 2 years. One year after the last teleroentgenogram was made she had a fulminating recurrence of rheumatic fever and died of pancarditis.

Thus, if one considers the entire group, the mortality rate is less than 3 per cent. If one considers only those cases in which the rheumatic infection was of sufficient severity to cause valvular damage, the mortality rate is still low, i.e., approximately 7 per cent.

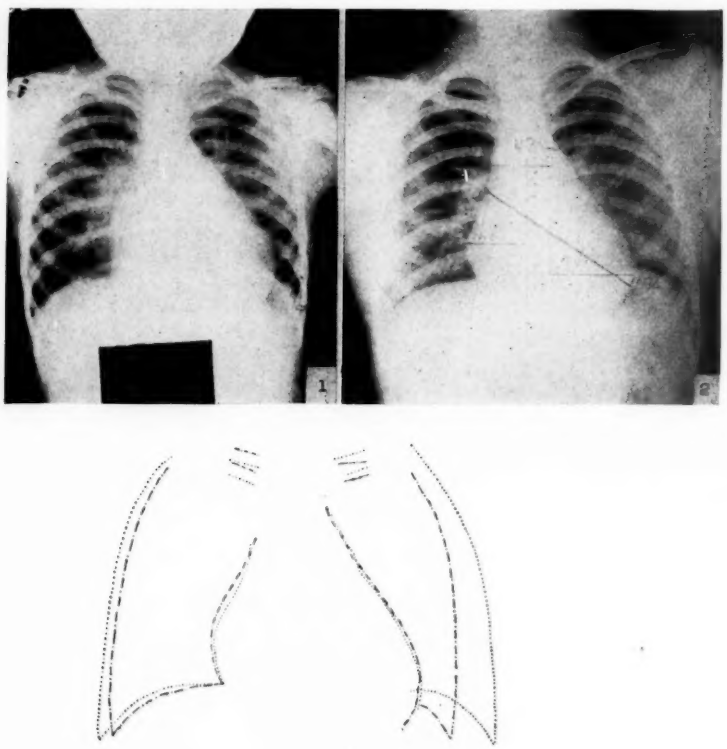


Fig. 3*a*.—Size of heart stationary; chest growing. Case 3 (mitral insufficiency). *1*, Teleroentgenogram 6/17/32. *2*, Teleroentgenogram 10/10/34. *3*, Tracings of teleroentgenograms 6/17/32 — . — . — . —, 10/10/34 . . . . . .

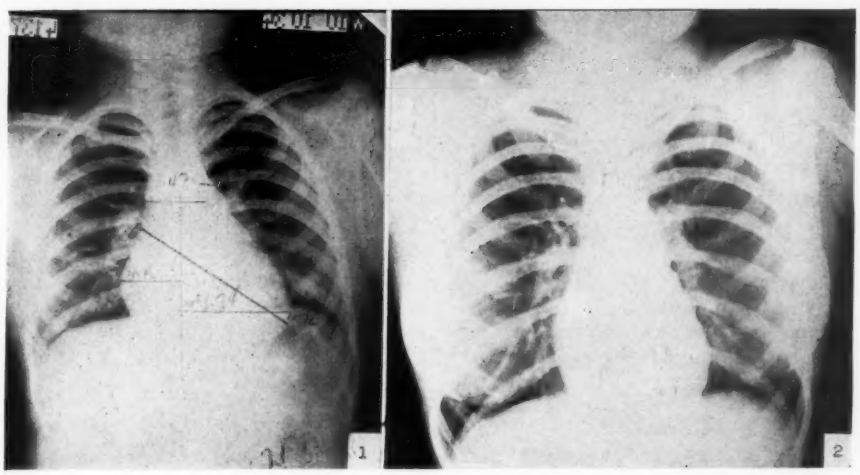
CASES IN WHICH THE HEART, AFTER AN INITIAL INCREASE IN SIZE, REMAINED STATIONARY WHILE THE CHEST GREW

This group of cases illustrates a phenomenon which is quite different from that of normal growth. In every instance the heart was enlarged

TABLE III

DATE	AGE (YR.)	HEART T.D. (CM.)	CHEST I.D. (CM.)	C/T	HEIGHT (IN.)	WEIGHT (LB.)	AV. T.D. OF HEART (CM.)	PER CENT DEVIATION FROM AV.
June, 1932	5	11.2	18.5	60.5		33	8.5	+30
September, 1933	6	10.9	19.6	55.6		58	8.6	+25
October, 1934	7	11.5	21.3	54.0		73	9.0	+26
April, 1936	9	10.5	23.4	44.8	58	85½	9.8	+ 7
August, 1936	9	10.5	23.4	44.8	59	84	9.9	+ 6
May, 1937	10	11.0	24.7	44.5	61	91	10.3	+ 7
December, 1938	11	10.6	24.7	42.9	61½	107½	11.2	- 5

T.D., Transverse diameter; I.D., internal diameter.



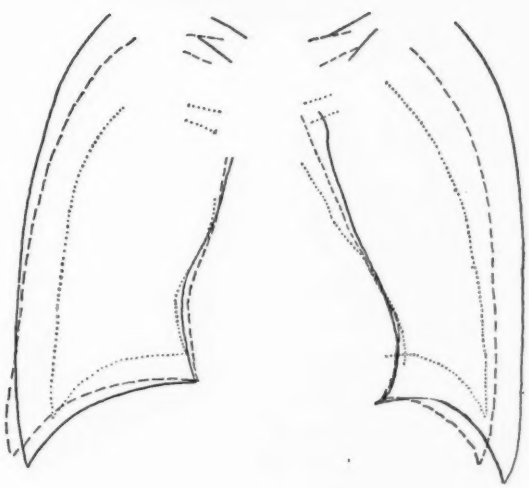


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Fig. 3*b*.—Size of heart stationary; chest growing. Case 3 (mitral insufficiency). *1*, Same as Plate *3a*, *2*. *2*, Teleroentgenogram 12/3/38. *3*, Tracings of teleroentgenograms 10/10/34 . . . . . (Same as . . . Plate 3*a*, *3*), 8/24/36 — — — — —, 12/3/38 ———.

when the patient first came under observation; thereafter, the size of the heart remained stationary while the chest grew. In a number of instances the result has been that the size of the heart eventually came to lie within normal limits. This phenomenon was new to us, and we believe that it is not generally appreciated. Therefore, a few illustrative cases are presented.

CASE 3.—D. W. (H.L.H. No. 77441), a white girl, was born in 1926. She was first brought to the Harriet Lane Home when she was 5 years of age, at which time she had a severe rheumatic infection, cardiac enlargement, tachycardia, gallop rhythm, and a pronounced mitral insufficiency. She remained in the hospital two months, and was then transferred to our convalescent home, where she remained three years, except that each summer she returned home for a short stay. This was permitted because her ultimate prognosis seemed so unfavorable. Throughout the three years she had fever and tachycardia; finally, in 1935, she was sent home to remain in bed. In May, 1936, four years after the onset, her sedimentation rate returned to normal, and she was allowed to get up gradually. In March, 1937, she had the "flu," which, in all probability, was a rheumatic exacerbation. She was put back to bed for several months. In November, 1938, she developed subacute bacterial endocarditis and died in April, 1939. At the autopsy the heart was described as "perhaps slightly enlarged."

The composite picture of the tracings of the teleroentgenograms is shown in Figs. 3*a* and 3*b*. The actual measurements of the transverse diameter of the heart and chest are given in Table III.

Figs. 3*a* and 3*b* (the dotted line in Fig. 3*b*, is the duplicate of the dotted line in Fig. 3*a*) illustrate how slight was the change in the size of the heart over the period of years. Ever since 1932, examination of the heart had shown definite signs of mitral insufficiency.

Although these teleroentgenograms show that the transverse diameter of the heart has varied slightly, on the whole it has remained remarkably constant, whereas the chest has grown steadily. During this period the child grew in stature and gained in weight. The cardiothoracic ratio fell from 60.5 to 42.9 per cent. The heart, which was originally 30 per cent larger than the theoretical normal for her age, was, at the time of her final illness, 5 per cent smaller than the average for her age, height, and weight.

In this case it is obvious that the heart did not enlarge progressively; indeed, the heart did not even increase in size in proportion to the growth of the child. On the contrary, the size of the heart remained relatively unaltered while the child grew.

CASE 4.—M. M. (H.L.H. No. 29031), a white boy, was born in 1921. He was first seen at the Harriet Lane Home in 1933. He gave the history that he had had his first attack of acute rheumatic polyarthritis in 1929, a second in 1931, and a third in 1932. In February, 1933, he had a fourth attack of polyarthritis. The following month he was brought to the hospital with severe pancarditis and pericardial effusion (these teleroentgenograms are not included). His heart appeared to be enlarged, and he had a systolic murmur, a mid-diastolic murmur, and gallop rhythm. He was in the hospital five weeks and was kept in bed for an additional

TABLE IV

DATE	AGE (YR.)	HEART T.D. (CM.)	CHEST I.D. (CM.)	C/T	HEIGHT (IN.)	WEIGHT (LB.)	AV. T.D. OF HEART (CM.)	PER CENT DEVIATION FROM AV.
March, 1933	12	12.0	24.3	49.0	55	66	9.5	+28
September, 1933	12	12.2	24.8	49.5	56	81½	9.6	+27
May, 1934	13	12.4	26.7	46.4	61½	106½	10.0	+24
							11.2	*+10*
July, 1936	15	12.3	28.0	43.9	63½	118½	10.4	+18
							11.5	*+ 7*
June, 1938	17	12.5	29.5	42.3	64½	128½	*12.0*	*+ 4*

T.D., Transverse diameter; I.D., internal diameter.
Italicized figures are those given by the insurance company.

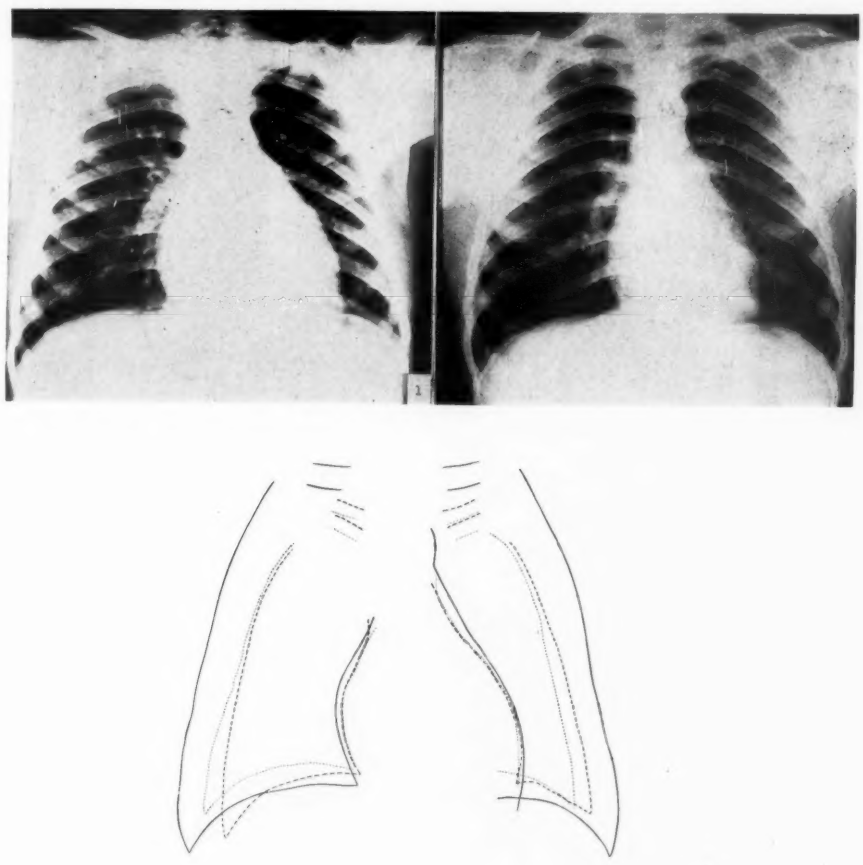


Fig. 4.—Size of heart stationary; chest growing. Case 4 (mitral insufficiency and mitral stenosis). *1*, Teleroentgenogram 3/30/33. *2*, Teleroentgenogram 6/24/38. *3*, Tracings of teleroentgenograms 3/30/33 . . . . . , 9/12/33 — — — — — , 6/24/38 ———.

three months. In October, 1933, he suffered from an exacerbation of his rheumatic infection, and was in bed one month. In July, 1934, he had his sixth attack of rheumatic polyarthritis; he was in bed four months and remained out of school throughout the year 1934-35. Since 1934 he has been well. He is now at work. His heart shows definite evidence of mitral insufficiency and stenosis.

The composite picture of the tracings of the teleroentgenograms is presented in Fig. 4. Table IV gives the actual measurements of the heart.

In this case the transverse diameter of the heart increased only 0.5 cm. over a period of five years; the internal diameter of the chest increased 5.2 cm. The cardiothoracic ratio dropped from 49 to 42.3 per cent.

CASE 5.—F. B. (H.L.H. No. 82392), a white boy, was born in 1922. He was first seen at the Harriet Lane Home in March, 1933, during his third attack of severe rheumatic polyarthritis. His first attack of rheumatic fever occurred in 1930, and his second in 1931. When brought to the dispensary he not only had polyarthritis, but also pancarditis and consolidation of the lung. On admission he had signs of pericardial effusion and pneumonia (therefore, no teleroentgenograms taken before October, 1933, are shown). He remained in the hospital two months and was in bed at home for eight months. During the spring of 1934 he was allowed to get up gradually; he finally returned to school in September, 1934. Since September, 1934, the boy has been well. He has had no recurrence. From 1931 to 1936 there was evidence of only slight mitral insufficiency; in December, 1936, he developed questionable signs of mitral stenosis. Both have persisted unaltered to date.

The composite picture of the tracings of the teleroentgenograms is presented in Fig. 5. The measurements are given in Table V.

In this case the measurements showed a maximum variation of 1.0 cm., and a difference of only 0.5 cm., between October, 1933, and December, 1938. Theoretically, the diameter of the heart should have increased 1 to 2 cm. The consequence of these changes is that, whereas, in 1933, the size of the heart was 18 per cent above the average for his age and height, in 1938 it was 12 per cent above the normal standard given by Ziskin, but only 1 per cent above that given by Ungerleider and Clark.*

CASE 6.—T. W. (H.L.H. No. 75770), a white boy, was born in 1922. He first came to the Harriet Lane Home, in 1932, because of chronic tonsillitis; his heart was entirely normal. He was next seen in July, 1934; at that time he stated that, in 1933, he had a severe attack of rheumatic fever, and was in St. Joseph's Hospital for four months. For nine months thereafter he was kept quiet and received digitalis. When he was examined in July, 1934, his heart was enormous, and there were definite signs of mitral insufficiency and stenosis. Since then he has remained well.

The composite picture of the tracings of the teleroentgenograms is presented in Fig. 6*a*, and the actual measurements of the heart are given in Table VI.

Lest it be thought that the size and contour of the heart in this case were such that further enlargement would not be discernible, the

*The boy was 68 inches tall, and of normal build. Ziskin's study did not include many children of this height. Therefore, we believe that the standards given by Ungerleider and Clark are probably more accurate than those of Ziskin.

TABLE V

DATE	AGE (YR.)	HEART T.D. (CM.)	CHEST I.D. (CM.)	C/T	HEIGHT (IN.)	WEIGHT (LB.)	AV. T.D. OF HEART (CM.)	PER CENT DEVIATION FROM AV.
October, 1933	11	11.4	23.4	48.7	57½	79	9.7	+18
July, 1934	12	11.8	25.7	45.9	60	88½	9.8	+20
							10.3	*+14*
December, 1936	14	12.4	28.8	43.1	67	122	10.6	+17
							11.4	*+ 9*
December, 1938	16	11.9	29.4	40.0	68	129	10.6	+12
							11.7	*+ 1*

T.D., Transverse diameter; I.D., internal diameter.
Italicized figures are those given by the insurance company.

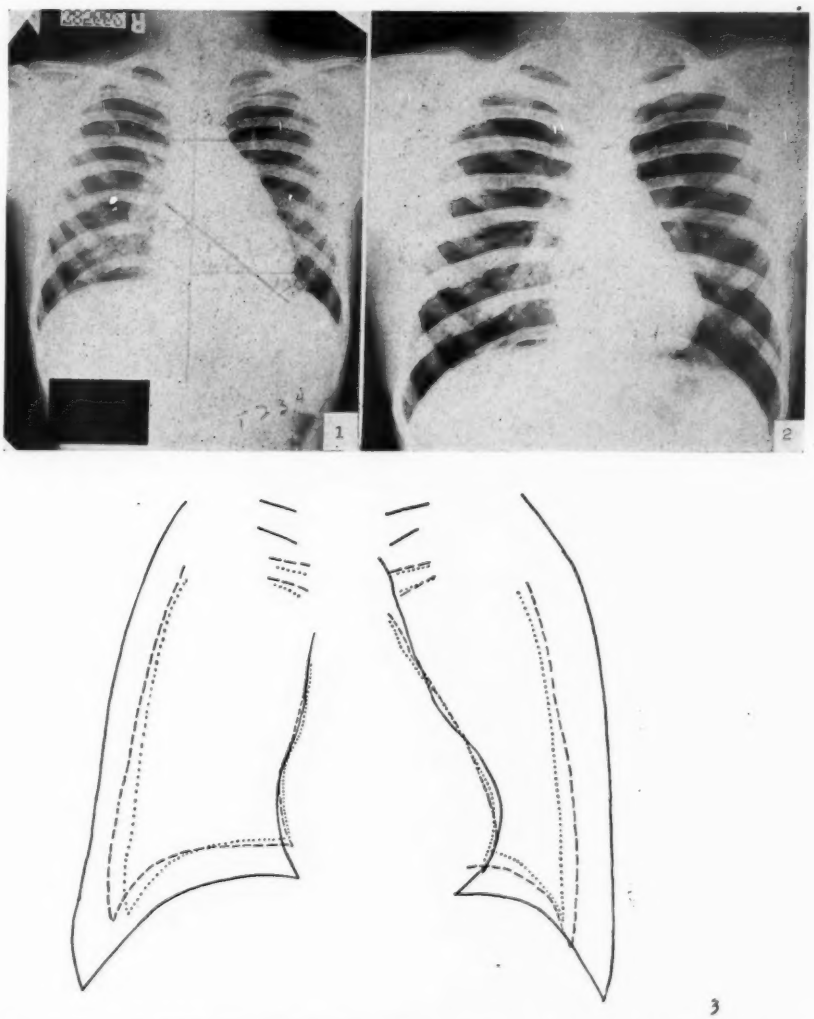


Fig. 5.—Size of heart stationary; chest growing. Case 5 (slight mitral insufficiency and questionable mitral stenosis). *1*, Teleroentgenogram 10/6/33. *2*, Teleroentgenogram 12/9/38. *3*, Tracings of teleroentgenograms 10/6/33 . . . . . , 7/6/34 — — — — — , 12/9/38 ————— .

TABLE VI

DATE	AGE (YR.)	HEART T.D. (CM.)	CHEST I.D. (CM.)	C/T	HEIGHT (IN.)	WEIGHT (LB.)	AV. T.D. OF HEART (CM.)	PER CENT DEVIATION FROM AV.
August, 1934	12	12.3	21.0	58.5	50	51½	9.6	+28
January, 1939	17	11.8	23.5	50.2	58	80	10.1	+17

T.D., Transverse diameter; I.D., internal diameter.

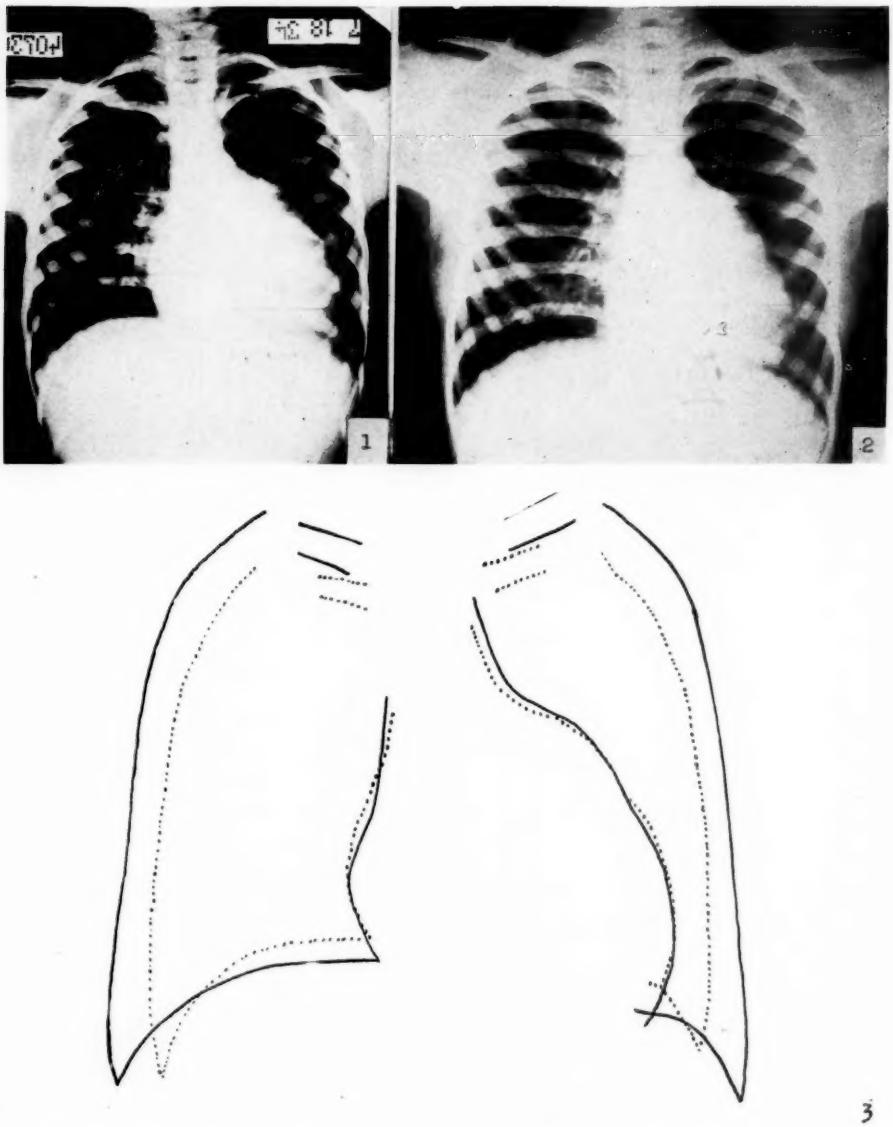


Fig. 6*a*.—Size of heart stationary; chest growing. Case 6 (mitral insufficiency and mitral stenosis). *1*, Teleroentgenogram 7/18/34. *2*, Teleroentgenogram 1/23/39. *3*, Tracings of teleroentgenograms 7/18/34 . . . . . , 1/23/39 ————— .

teleroentgenograms of another patient with severe rheumatic infection and mitral insufficiency and stenosis are presented in Fig. 6*b*.

In the latter case, although the transverse diameter of the heart did not increase, it is clear that the surface area enlarged.

These cases suffice to illustrate the phenomenon. Although there was slight variation in the size of the heart, the trend is perfectly clear;

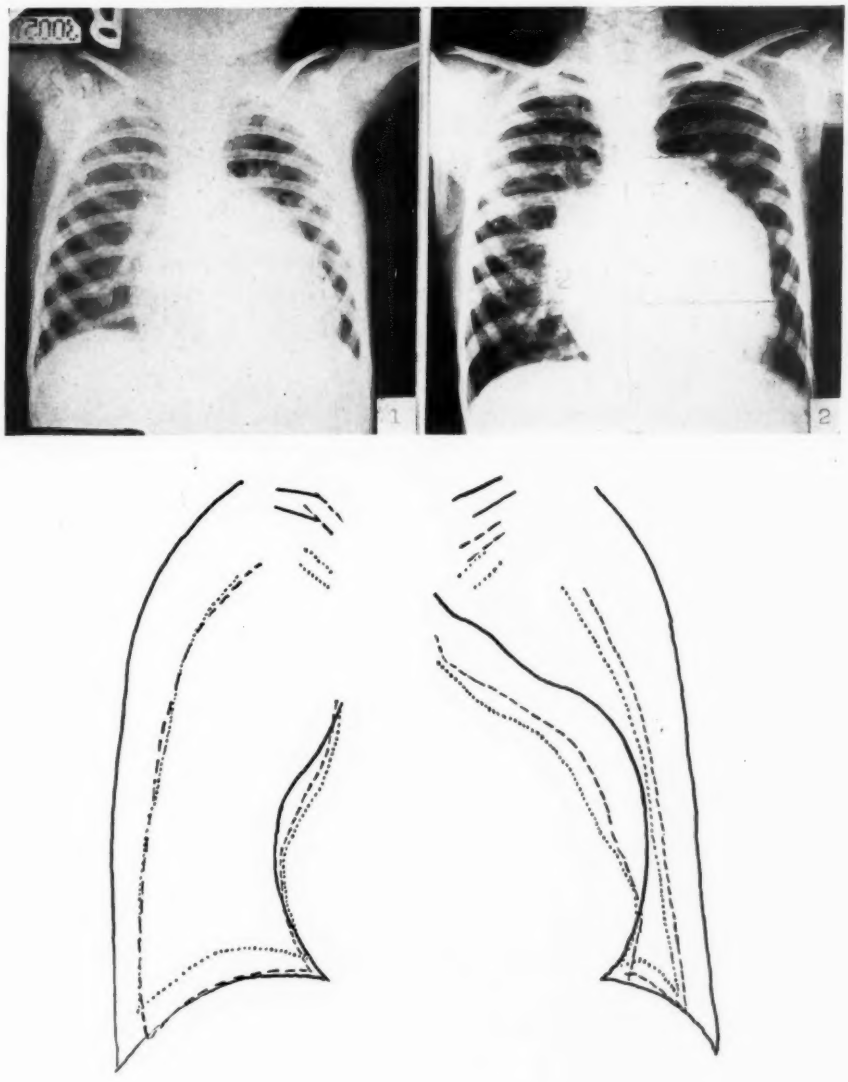


Fig. 6*b*.—Progressive cardiac enlargement. Case of mitral insufficiency and mitral stenosis. *1*, Teleroentgenogram 11/10/30. *2*, Teleroentgenogram 3/9/36. *3*, Tracings of teleroentgenogram, 11/10/30 . . . . . , 1/5/31 — — — — —, 3/9/36 ————.

broadly speaking, the size of the heart remained constant and the chest grew, with the result that the cardiothoracic ratio decreased.

The fact that the heart was enlarged when the patient first came under observation is a clear indication that there had been previous cardiac strain. In most cases, cardiac enlargement is caused by a combination of dilatation and hypertrophy. Therefore, it is natural that in some cases there was a decrease in the size of the heart before the size became stationary. Furthermore, in a few cases we have seen an

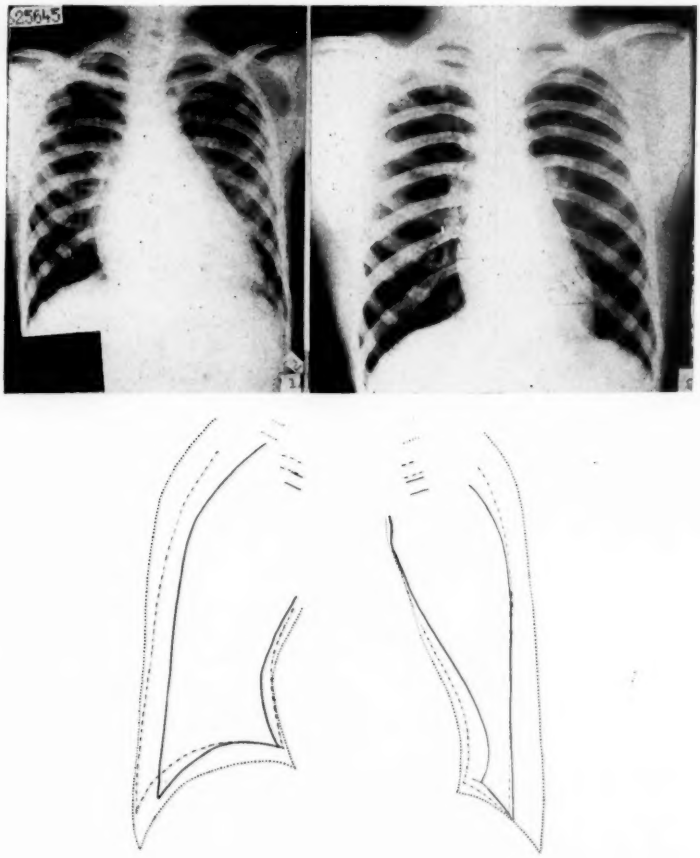


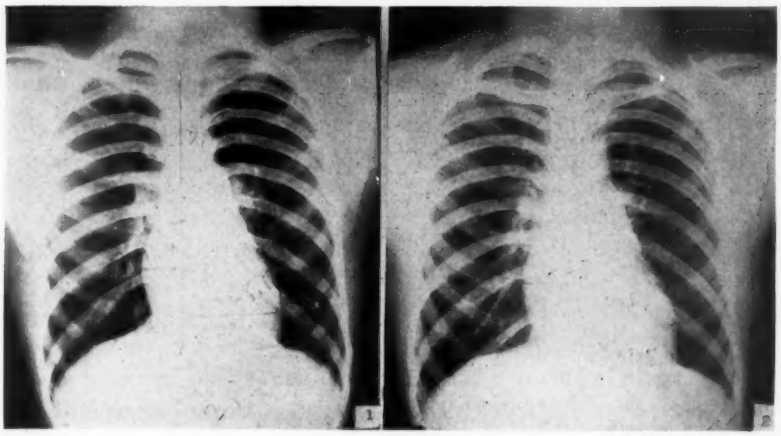
Fig. 7*a*.—Heart decreased in size. Case 7 (mitral insufficiency and mitral stenosis). *1*, Teleroentgenogram 8/13/31. *2*, Teleroentgenogram 3/25/35. *3*, Tracings of teleroentgenograms 8/13/31 ————, 6/10/32 — . — . —, 3/25/35 . . . . . .

additional phenomenon; namely, after the chest had grown sufficiently so that the size of the heart was relatively normal, the heart again increased in size as the chest grew. As is to be expected, this phenomenon was observed in cases in which the heart was not enormously enlarged, and therefore the patient did not have to attain his full growth to enable the size of the heart to return to normal proportions. The following case is an excellent illustration.

TABLE VII

DATE	AGE (YR.)	HEART T.D. (CM.)	CHEST I.D. (CM.)	C/T	HEIGHT (IN.)	WEIGHT (LB.)	AV. T.D. OF HEART (CM.)	PER CENT DEVIATION FROM AV.
August, 1931	13	14.6	22.5	64.8	60	71	9.9	+47.4
October, 1931	13	15.0	22.7	66.1	60	68½	9.9	+51.5
June, 1932	14	12.5	23.5	53.1	60	96	10.2	+21
							10.7	*+17*
May, 1934	16	12.2	26.0	46.9	66½	117	10.6	+14
							11.2	*+ 9*
March, 1935	17	12.2	25.8	47.6	67½	121½	*11.4*	*+ 7*
March, 1936	18	12.8	27.0	47.4	67½	120½	*11.4*	*+12*
June, 1937	19	12.9	27.5	46.9	67½	130	*11.7*	*+10*
May, 1938	20	12.6	27.3	46.1	68½	136½	*12.0*	*+ 5*
January, 1939	21	13.2	27.0	48.8	68	145½	*12.4*	*+ 7*

T.D., Transverse diameter; I.D., internal diameter.
Italicized figures are those given by the insurance company.



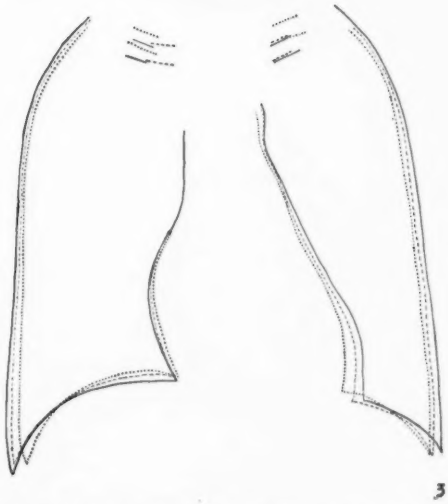


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Fig. 7*b*.—Normal growth. Case 7 (mitral insufficiency and mitral stenosis). *1*, Same as Plate 7*a*, *2*. *2*, Teleroentgenogram 1/11/39. *3*, Tracings of teleroentgenograms 3/25/35 . . . . . (Same as . . . Plate 7*a*, *3*), 6/2/37 — — — — — , 1/11/39 ———— .

CASE 7.—F. S. (H.L.H. No. 73438), a white boy, was born in 1919. He had scarlet fever at the age of 10 years. His first known rheumatic attack occurred in 1931, when he was brought to the hospital because of dyspnea and abdominal pain. His heart was enlarged; he had a definite mitral insufficiency and a mid-diastolic murmur. His liver extended nearly to the umbilicus. He stayed in the hospital one month, and was then transferred to a convalescent home where he remained five months. Throughout the following year his activity was restricted. By August, 1934, he had developed a definite mitral stenosis. In February, 1935, and again in September, 1938, he had capillary bronchitis. Aside from these two illnesses he has been well and is leading a normal life.

The composite picture of the tracings of the teleroentgenograms is presented in Figs. 7*a* and 7*b*. Table VII gives the actual measurements of his heart.

This patient's heart, which was definitely slightly enlarged in August, 1931, and was still the same size in October, 1931, had decreased in size when he returned from the convalescent home in May, 1932. Between 1932 and 1935 the size of the heart remained stationary. Indeed, in 1935 the heart was slightly smaller than it had been in 1932. Between 1935 and 1939 the gradual increase in the size of the heart was consistent with the growth of the body.

In this case the presumptive evidence is that, at the time of the acute attack, part of the enlargement was caused by dilatation. When the dilatation subsided, the "hypertrophy" remained. Finally, when the growth of the body became commensurate with that of the heart, both grew normally.

In all of the cases so far cited, it is obvious that we failed to observe the patient during the period when the heart was enlarging. We have, however, studied this in a number of other cases. In some there has been progressive cardiac enlargement; this group we shall discuss presently. In others the enlargement occurred at irregular intervals.* In three cases we observed, first, an increase in the size of the heart and then a decrease; and thereafter, over a period of years, the size of the heart remained stationary. One patient had mitral insufficiency and mitral stenosis; another had aortic insufficiency; and a third, at the present time, has no demonstrable valvular lesion. The sequence of events in the third case clearly illustrates the phenomenon. The history is as follows:

CASE 8.—E. H. (H.L.H. No. 65899), a colored boy, was born in 1920. In 1929 he had "grippe," and complained of shortness of breath. In February, 1930, he was first seen at the Harriet Lane Cardiac Clinic, and was found to have rheumatic heart disease, as evidenced by a harsh systolic murmur which was well transmitted to the axilla, and a mid-diastolic murmur. Rest in bed was recommended, but unfortunately he was lost sight of until September, 1930, when he was admitted to the hospital because of cardiac failure. After his discharge from the hospital he was followed in the clinic for two months; then he moved to New York. When he was next seen, in March, 1931, he had polyarthritis, numerous extrasystoles, and congestive heart failure. During the next eight months he had three attacks of heart

*These cases will be reported later.

failure which required hospitalization for three months, two months, and two months, respectively. During the third admission he received digitalis. It was not until October, 1931, that he was sufficiently improved to be cared for at home. At that time he had a harsh systolic murmur which was well transmitted to the axilla, a short mid-diastolic murmur at the apex, and many extrasystoles; the latter persisted for six months. During 1932 and 1933 his activity was greatly restricted. During the next two years the physical signs of his heart disease became progressively less apparent, and, in 1935, only a soft apical systolic murmur remained. It was not until then that the administration of digitalis could be stopped without causing cardiac dilatation. Since that time he has been well.

The composite picture of the tracings of the teleroentgenograms is presented in Fig. 8*a* and 8*b*. Table VIII gives the actual measurements of his heart.

Fig. 8*a* (*3*) shows the increase* in the size of the heart and the decrease in size which followed the administration of digitalis. Fig. 8*b*, in which the dotted line is a duplicate of that in Fig. 8*a*, illustrates that after this decrease, the size of the heart remained remarkably constant. From November, 1932, to November, 1938, the transverse diameter of the heart remained virtually stationary, whereas that of the chest increased 5.0 cm. The consequence is that the cardiothoracic ratio decreased from 61.3 to 50 per cent. At the present time there are no murmurs; the heart remains slightly enlarged, but, in comparison with the previous plates, the change is remarkable.

The phenomenon of cardiac dilatation during an acute rheumatic infection is familiar to all. The two cases just cited illustrate how long the dilatation may last. Further, after the dilatation has subsided, the heart may remain enlarged.

Still more important is the fact, which is illustrated by the entire series of cases, that, after the heart has enlarged, the factors which caused the enlargement may disappear and the heart may cease to enlarge. Indeed, it is possible for the size of the heart to remain stationary while the chest grows.

We have observed this phenomenon in twenty-four cases. Five patients, when last seen, had no demonstrable residual valvular damage; six had mitral insufficiency; six, mitral insufficiency and stenosis; one, questionable mitral stenosis; three, aortic insufficiency; and three, aortic insufficiency, mitral insufficiency, and probably mitral stenosis. In 50 per cent, with the growth of the patient the cardiothoracic ratio eventually became 45 per cent or less.

Clinically, the course of the disease in these cases was remarkably satisfactory. By and large, these children did well. Although most of them had more than one attack of acute rheumatic fever before coming under observation, the majority have had no recurrences since that time.

*Inasmuch as the tremendous increase in the size of the heart raises the question of pericardial effusion, it is worthy of note that none of the doctors on the pediatric or medical service of the Johns Hopkins Hospital who saw the patient thought that there was any evidence of pericardial effusion.

TABLE VIII

DATE	AGE (YR.)	HEART T.D. (CM.)	CHEST I.D. (CM.)	C/T	HEIGHT (IN.)	WEIGHT (LB.)	AV. T.D. OF HEART (CM.)	PER CENT DEVIATION FROM AV.
October, 1930	10	12.9	22.6	57.1	56½	74	9.6	+34
June, 1931	11	17.9	22.7	79.0	58	86½	9.6	+86
November, 1931	11½	14.4	23.2	61.6	58½	86	9.6	+50
April, 1932	12	14.1	23.0	61.3	59	99½	10.0	+41
November, 1932	12	13.5	24.0	56.2	61½	113½	10.5	+28.5
							11.5	*+17*
August, 1933	13	13.9	24.7	57.5	63½	120	10.7	+30
							11.7	*+19*
March, 1934	14	14.6	26.5	55.1	67	140	10.7	+35
							12.3	*+19*
November, 1938	18	14.0	28.0	50.0	70½	164	*13.0*	*+ 7.5*

T.D., Transverse diameter; I.D., internal diameter.
Italicized figures are those given by the insurance company.

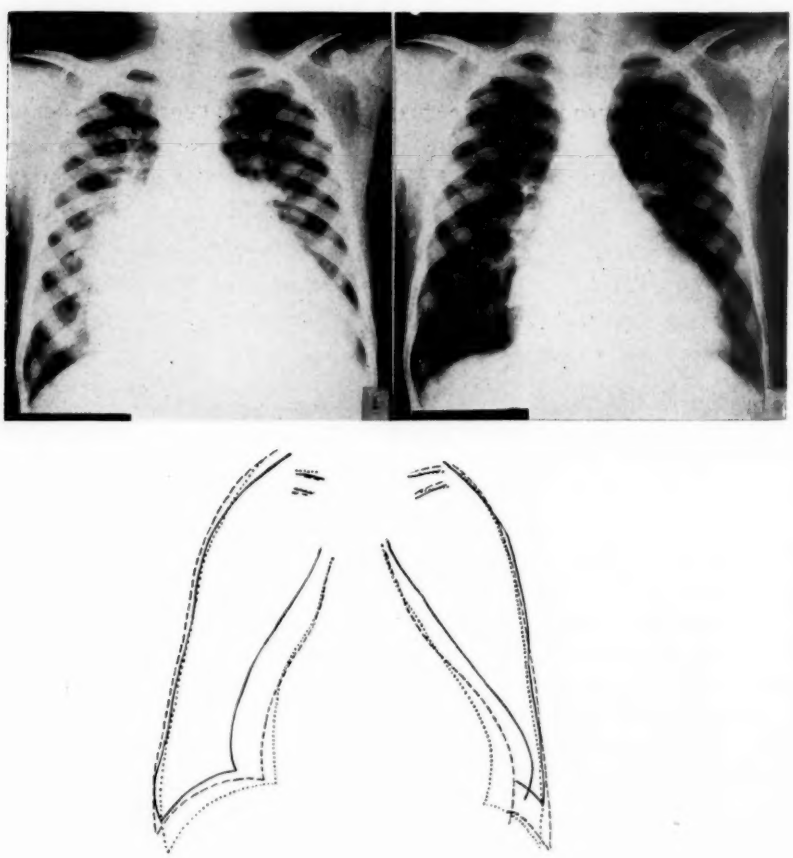


Fig. 8*a*.—Heart enlarged and decreased in size. Case 8 (severe rheumatic heart disease). *1*, teleroentgenogram 6/13/31. *2*, Teleroentgenogram 11/6/31. *3*, Tracings of teleroentgenograms 10/15/30 . . . . . , 6/13/31 ———— , 11/6/31 — — — — —.

Six of the children, however, did have recurrences during the period in which the size of the heart remained stationary, and, in addition, in one case (Case 3) the hypertrophy ceased, in spite of the fact that the rheumatic infection remained active for three years. It is worthy of note that all of these children, with the exception of the child who insidiously developed questionable signs of mitral stenosis, were kept at complete bed rest throughout the period of active infection.

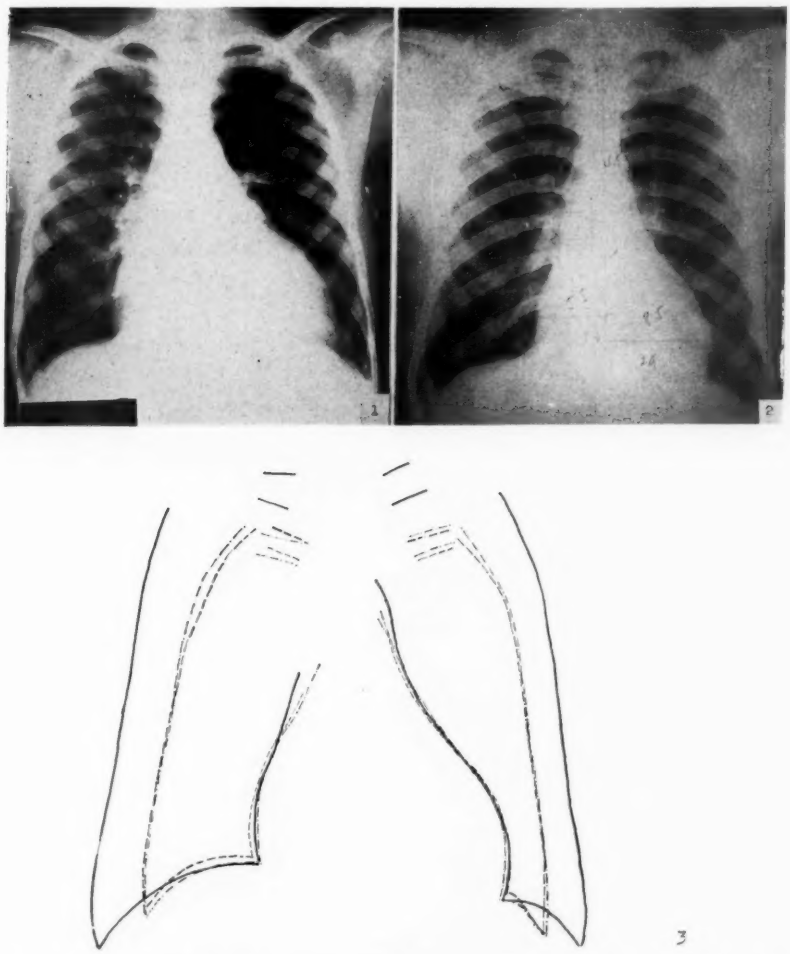


Fig. 8*b*.—Heart stationary and chest growing. Case 8 (severe rheumatic heart disease). *1*, Same as Plate 8*a*, *2*. *2*, Teleroentgenogram 4/25/32. *3*, Tracings of teleroentgenograms 11/6/31 — — — — — (Same as — — — Plate 8*a*, *3*); 4/25/32 — . — . — ; 11/2/38 ————.

In this entire group there were but three deaths—two from subacute bacterial endocarditis and one from acute rheumatic fever. The latter occurred in the case of a boy who had had a severe infection which had resulted in tremendous cardiac enlargement, pronounced aortic in-

sufficiency, and clinical signs of adhesive mediastinitis. For three years the size of the heart remained stationary while the chest grew, and the cardiothoracic ratio decreased from 64 to 60 per cent. The following year he developed rheumatic pancarditis and died.

The mortality rate in this group was low, namely, 12.5 per cent. Two children (approximately 10 per cent) still show signs of active rheumatic infection, and are at rest in bed. The remaining children (77.5 per cent) show no signs of rheumatic activity, and are leading normal, active lives.

PROGRESSIVE CARDIAC ENLARGEMENT

The third group showed an entirely different phenomenon. In these cases, the heart, which was already enlarged when the patient first came under observation, continued to enlarge progressively. We have observed this sequence of events in sixteen cases. From this group we excluded not only all cases of pericardial effusion, but also all cases in which there was any evidence of adhesive mediastinitis. Exclusion of the latter was deemed advisable because of the possibility that adhesion between the heart and the chest might cause cardiac enlargement. The phenomenon of progressive cardiac enlargement is familiar. Two cases will suffice as illustrations.

CASE 9.—A. C. (H.L.H. No. 56627), a colored girl, was born in 1928. In January, 1933, she first complained of joint pains. She was not seen, however, until June, 1933, at which time she had severe heart failure. Her heart was enormously enlarged, and she had a systolic murmur and a mid-diastolic murmur. She was in the Provident Hospital for three months. Her first stay at the Harriet Lane Home lasted from September, 1933, to March, 1934. Throughout the next four years she had repeated exacerbations of rheumatic fever which necessitated readmission to the hospital. In March, 1938, she died. Autopsy showed chronic rheumatic heart disease, with Aschoff bodies throughout the myocardium.

The composite picture of the tracings of the teleroentgenograms is presented in Fig. 9. The actual measurements of the size of the heart and the size of the chest are given in Table IX.

It is clear that, in this case, the heart increased in size more rapidly than the chest. Case 10 illustrates the same phenomenon.

CASE 10.—D. H. (H.L.H. No. 52720), a colored girl, was born in 1925. She was first examined in 1932, because of tuberculosis. A teleroentgenogram which was taken at that time showed a small heart; the cardiothoracic ratio was 42.0 per cent. In the spring of 1937 she apparently had her first attack of acute rheumatic fever. At that time the size of her heart was found to be within the upper limits of normal, and the murmur was regarded as functional. She was lost sight of for a year. In June, 1938, she returned with the complaint that one of her knees had been swollen for two months. Her heart was found to be enlarged, and she had a harsh, blowing systolic murmur and a mid-diastolic murmur. Rest in bed was advised, but it was impossible to obtain the cooperation of the patient.

TABLE IX

DATE	AGE (YR.)	HEART T.D. (CM.)	CHEST I.D. (CM.)	C/T	HEIGHT (IN.)	WEIGHT (LB.)	AV. T.D. OF HEART (CM.)	PER CENT DEVIATION FROM AV.
December, 1933	5	12.8	19.5	65.6		44½	8.5	+50
June, 1934	6	12.3	19.5	63.0	45	51	8.6	+46.5
October, 1935	7	14.7	21.6	68.6	50½	64	9.2	+60
March, 1936	8	14.6	22.2	65.7	50½	71½	9.2	+60
November, 1937	9	16.0	22.0	71.1	52½	65½	9.3	+72
February, 1938	10	15.2	22.5	67.5	53	67	9.5	+60

T.D., Transverse diameter; I.D., internal diameter.

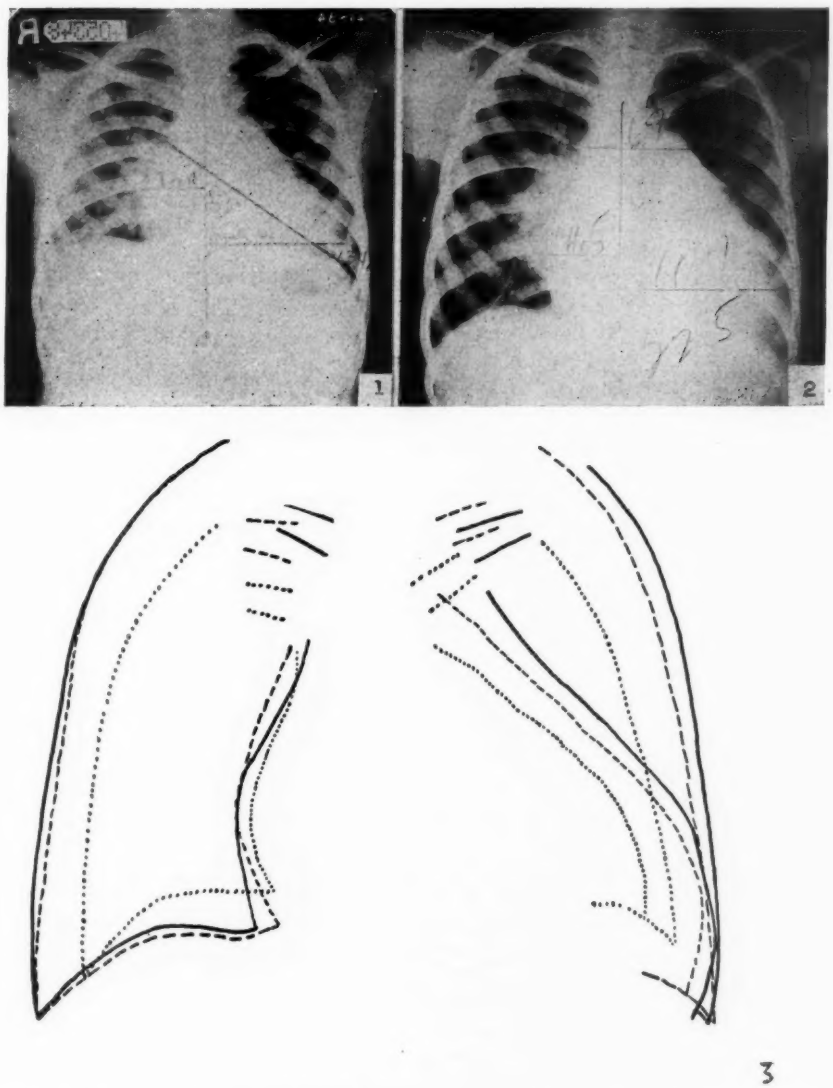
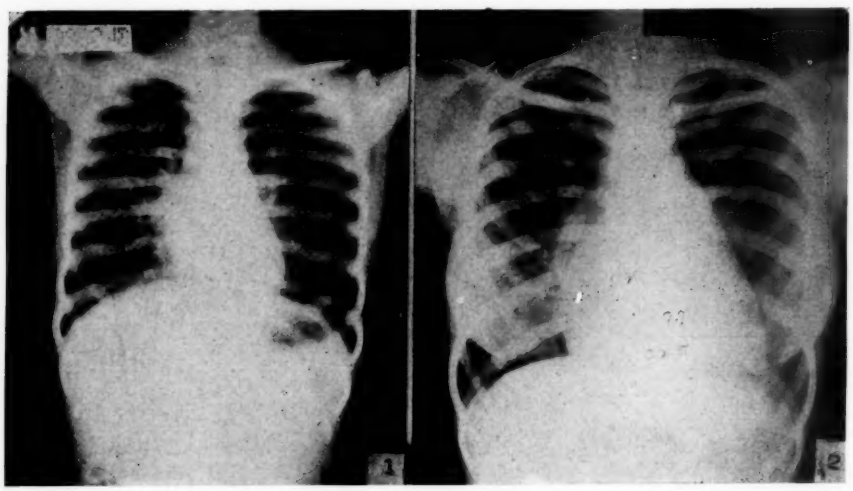


Fig. 9.—Progressive cardiac enlargement. Case 9 (rheumatic myocarditis, with slight mitral insufficiency). *1*, Teleroentgenogram 6/21/34. *2*, Teleroentgenogram 2/4/38. *3*, Tracings of teleroentgenograms 6/21/34 . . . . . , 3/13/36 — — — — — , 2/4/38 ————— .

TABLE X

DATE	AGE (YR.)	HEART T.D. (CM.)	CHEST I.D. (CM.)	C/T	HEIGHT (IN.)	WEIGHT (LB.)	AV. T.D. OF HEART (CM.)	PER CENT DEVIATION FROM AV.
May, 1932	7	7.3	17.0	42.0			9.0	−19
July, 1937	12	9.9	20.2	48.5		52½	9.8	+14
November, 1938	13	12.2	21.1	57.6	57	72½	9.8	+24.4
February, 1939	14	13.0	22.0	59.1	58	78	10.0	+30

T.D., Transverse diameter; I.D., internal diameter.



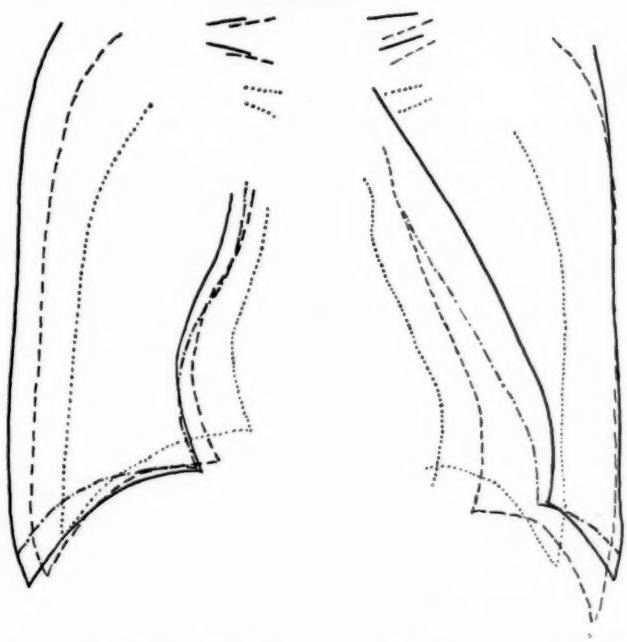


Fig. 10.—Progressive cardiac enlargement. Case 10 (mitral insufficiency and questionable mitral stenosis). *1*, Teleroentgenogram 5/17/32. *2*, Teleroentgenogram 2/17/39. *3*, Tracings of teleroentgenograms 5/17/32 . . . . . , 7/28/37 — — — — — , 11/30/38 — . — . — , 2/17/39 ————— .

The composite picture of the tracings of the teleroentgenograms is presented in Fig. 10. The actual measurements of the size of the heart and the size of the chest are given in Table X.

This case not only illustrates the rapidity with which the heart may enlarge, but, also, a comparison with the first teleroentgenogram, which was taken before the onset of rheumatic fever, illustrates how great the cardiac enlargement may become before it exceeds the theoretical upper limit of normal.

Obviously, these teleroentgenograms show a sequence of events which is quite different from that in either of the two preceding groups. The time required for the enlargement to develop varied from six months to five years. In cases of gradual progressive enlargement, it is clear that the heart enlarged out of proportion to the growth of the chest.

The type and severity of the valvular lesions in this group do not differ greatly from those in the preceding group. Two patients had mitral insufficiency; three, mitral and aortic insufficiency; two, mitral insufficiency and slight mitral stenosis; five, mitral insufficiency and definite mitral stenosis; and one, mitral and aortic insufficiency and stenosis. In two cases the rheumatic infection was believed to be superimposed upon a congenital malformation of the heart, namely, an interauricular septal defect. Another child may also have congenital malformation, for the murmur was first heard when he was 15 months of age; at the present time, however, his physical signs are characteristic of mitral insufficiency and mitral stenosis.

Clinically, the course of the disease in this group was profoundly different from that in either of the two preceding groups. Eight of the sixteen patients died, all of active rheumatic infection. In six of the cases the diagnosis was confirmed by autopsy. Although, in the other two, no autopsy was done, both children died of pancarditis. Of the remaining children, four are chronic invalids, and two have no complaints but still show evidence of an active rheumatic infection. The two remaining children have had repeated exacerbations of rheumatic fever, with only brief periods when they were free from infection.

Thus, among the children who showed progressive cardiac enlargement, the mortality rate was 50 per cent; in addition, 25 per cent are chronic invalids. The remaining 25 per cent, although they are not critically ill, have had repeated attacks of rheumatic fever, or have shown laboratory evidence of a persistently active infection.

DISCUSSION

These studies illustrate that there are at least three different and distinct sequences of events relative to the size of the heart in acute rheumatic fever. First, a heart which has never been enlarged may

show normal growth. Second, after a period of initial enlargement, it is possible for the heart to remain stationary in size while the chest grows. Third, there may be progressive cardiac enlargement.

The fact that the changes in the size of the heart may show different sequences in cases in which the valvular lesions are similar indicates that the valvular lesions are not the prime cause of cardiac enlargement. Indeed, in the first group, there were a number of subjects with persistent valvular damage whose hearts had never been enlarged; the increase in the size of their hearts was commensurate with normal growth. For example, in Case 2 the signs of aortic insufficiency persisted for seven years without demonstrable alteration in the size of the heart. In the second group, i.e., those patients in whom hypertrophy ceased, the majority of the patients showed definite signs of chronic valvular damage. These observations are in accord with the opinion expressed by Lewis,[5] namely, that the valvular lesion is of far less importance than the condition of the myocardium.

Lewis[5] and Palmer[2] have shown that, in adults, the heart enlarges as the result of an increase in the cardiac load and that, once the heart has adjusted itself to the new conditions, no further enlargement occurs. A notable example of this phenomenon is coarctation of the aorta; in spite of the persistent, sometimes extreme, hypertension, the heart does not undergo progressive enlargement. Our studies indicate that, fundamentally, the same is true in children with rheumatic fever, i.e., that cardiac enlargement occurs during periods of active rheumatic infection, and that, when the infection has subsided and the heart has adjusted itself to the valvular lesions, there is no further increase in the size of the heart other than that which is commensurate with normal growth.

The next question which presents itself is concerned with the relation of acute myocarditis to the increase in the size of the heart. All of our patients who showed cardiac enlargement had had an active rheumatic infection. Further, all those who showed progressive cardiac enlargement had signs of a persistent, active infection. The reverse is not true. Not all patients with an active infection have shown progressive cardiac enlargement. On the contrary, some never had demonstrable cardiac enlargement, and, in other cases, the enlargement ceased to exist.

The fact that cardiac enlargement can cease to exist although the active infection persists indicates that cardiac enlargement depends not only on the severity and duration of the disease, but also, in many instances, upon the work demanded of the diseased heart. For example, in Case 3, although the signs of active infection persisted for three years, the heart ceased to enlarge when the patient was put to bed.

It seems to us highly significant that, in every instance, with the exception of the child in the first group who insidiously developed signs of

mitral stenosis, all of the patients who had active rheumatic infection without demonstrable increase in the size of the heart were kept at complete bed rest throughout the active infection. This observation is the more significant because these cases were grouped solely on the basis of changes in the teleroentgenogram. After so doing, it was found that the children in whom cardiac enlargement came to an end were those who had had long periods of rest in bed. Although one cannot prove that rest was the decisive factor, the above observation strongly suggests that the degree of cardiac enlargement can be altered by treatment with rest in bed.

Inasmuch as, in a number of cases, signs of active rheumatic infection persisted for months after the heart ceased to enlarge, we believe that cardiac enlargement depends, to a large extent, on the load placed upon the heart during the period in which it is weakened by the acute or subacute myocarditis. It appears that the diseased heart is frequently unable to carry the load caused by ordinary physical exertion, and therefore undergoes hypertrophy. In such cases, if the patient is put to bed and the work required of the heart is thus lessened, the heart ceases to hypertrophy.

How great the enlargement may be is illustrated by the fact that, after the infection has subsided, the heart may be sufficiently large to meet the needs of the body for a number of years (for example, in Case 8, for six years). Under these circumstances there is no further increase in the size of the heart even when the patient is still growing, and is leading a normal, active life. It seems that, when the factors which caused cardiac enlargement cease to operate, the stimulus to the growth of that organ is withdrawn until such time as the growth of the body has become commensurate with that which occurred in the heart during the period of unusually great strain; thereafter there is a resumption of the normal rate of growth. Case 7 illustrates this phenomenon. This observation suggests that there is no essential difference between "hypertrophy" of the heart in response to an abnormal stimulus and normal "growth." It appears to be fundamentally a question of *rate* of growth.

Another illustration of this phenomenon was found in two cases in which the patients were followed over a period of years, and ultimately died. Both children, when they were first seen, had severe rheumatic infections, and their hearts were 30 per cent above the normal size for their age and height. Case 3 records the history of one of these children. In each instance, over a period of years, the heart remained stationary in size and the child grew, with the result that the size of the heart again came to lie within normal limits. Subsequently, each developed a *Streptococcus viridans* infection. At autopsy the hearts were found to be of approximately normal size; had either of the children died at an earlier date, the heart would have been described as "large for a child."

These observations afford confirmatory evidence of the validity of the observations based on teleroentgenograms.

The sequence of events is not always as clear as in the cases here reported. We have observed a large number of cases in which there was a slight increase or slight decrease in the size of the heart. In such cases it is difficult, if not impossible, to ascertain whether the decrease in size was a chance variation or whether the slight increase was caused by dilatation. In other cases, after the heart had enlarged, it remained stationary in size and then enlarged again. These cases will be reported later.

The observations reported in the present paper, although of a different nature, are in accord with those of Bland, Jones, and White[6] concerning disappearance of the physical signs of rheumatic heart disease. Their observations were based on physical examination and did not include teleroentgenograms. Case 8 illustrates the phenomenon reported by them. This boy had, for many years, both a harsh systolic murmur and a long mid-diastolic murmur; eventually both murmurs disappeared. The case is in no sense unique. It is, however, a dramatic example of the amount of improvement which is possible, even after repeated attacks of acute rheumatic fever. Our studies bring to light an additional factor; not only may murmurs disappear, but "hypertrophy" may also disappear.

Our third group of cases, in which there was progressive cardiac enlargement, illustrates a more familiar sequence of events—so familiar, in fact, that it is often considered inevitable. The children in this group suffered from severe infection of long duration. The severity of the infection is undoubtedly of great importance. Nevertheless, inasmuch as many patients in the second group also suffered from protracted, severe infections, it seems probable that one important reason for the unfavorable outcome in the third group was unrestricted activity. Some children undoubtedly have such a severe infection that rest in bed will not alter the course of the disease. Nevertheless, it seems to us highly significant that only 50 per cent of the children in the third group were kept in bed, and these for only short periods during the acute stage of their illness. The remainder had no rest in bed until their terminal illness.

The high mortality rate and the high incidence of chronic invalidism in the third group indicate all too clearly the serious prognosis in those cases in which there is progressive cardiac enlargement. In this group the mortality rate was 50 per cent, and an additional 25 per cent are chronic invalids. These figures present a striking contrast to the course of the disease in the two preceding groups, in which the mortality rate was approximately 10 per cent; an additional 10 per cent still have active infections, but 80 per cent of the children are well and are leading active lives.

These differences in the mortality rate speak for themselves. There is no question as to the goal for which one should strive. If successive teleroentgenograms indicate that the size of the heart has increased out of proportion to the growth of the child, it is clear evidence of an unfavorable sequence of events. It is, in itself, presumptive evidence that the child suffers from an active infection. Certainly, under such circumstances the work demanded of the heart should be kept at a minimum by rest in bed. Once the infection has been overcome, the heart readily adjusts itself to the increased load caused by the valvular damage, and thereafter there should be no further cardiac enlargement. For such patients the outlook is excellent; they may hope to lead normal, active lives.

CONCLUSIONS

1. By superimposing teleroentgenograms, one may obtain valuable information concerning the course of a rheumatic infection.

2. This method of study has revealed three distinct kinds of changes in the size of the heart: (1) It may grow normally; (2) it may, after a period of enlargement, remain stationary in size while the chest grows; and (3) it may enlarge progressively.

3. These observations prove that, in the course of the rheumatic infections, cardiac enlargement is not an inevitable, gradual, progressive process; even in the presence of valvular damage, enlargement can occur and then cease.

4. The fact that all types of valvular lesions were found in our second and third groups indicates that the size of the heart does not depend primarily on the nature of the valvular lesion.

5. Evidence is brought forward that cardiac enlargement is directly related to activity of the rheumatic infection.

6. The fact that, in some cases, in spite of severe infection, the heart did not enlarge proves that active rheumatic infection does not inevitably cause cardiac enlargement.

7. Inasmuch as, in the majority of cases in which there was no cardiac enlargement during known periods of active infection, the patients were kept at complete bed rest, the load placed on the heart during the active infection must be an important factor.

8. The mortality rate among the patients who showed progressive cardiac enlargement was much higher than in the other two groups. In the first two groups the mortality rate was 7 to 13 per cent; 80 per cent of the patients are well. In the third group the mortality rate was 50 per cent; in addition, 25 per cent of these patients are chronic invalids; in only 25 per cent of the cases is the condition of the patient in any sense satisfactory.

9. The occurrence of progressive cardiac enlargement in the course of rheumatic fever is a serious phenomenon. It is strong presumptive

evidence of the existence of a persistent active infection and is a clear indication that the load on the heart should be reduced to a minimum by keeping the patient at complete bed rest.

10. Once the rheumatic activity has subsided and the heart has adjusted itself to the valvular lesions, there should be no further cardiac enlargement other than that which is commensurate with normal growth.

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DISCUSSION

DR. M. A. KUGEL, Miami Beach, Florida.—I want to thank Dr. Taussig very much for her report on enlargement of the heart. I think this problem becomes simpler when we appreciate the physiologic mechanism involved. All agree that an enlarged heart usually gives more concern than a heart that is not enlarged. We can go back to the work of Müller, and many others, who studied the inflow and outflow tracts, for enlightenment as to the causes of cardiac enlargement. The heart does not enlarge beyond normal limits unless there is some underlying pathologic-physiologic disturbance. If the myocardium is normal, under certain conditions only hypertrophy develops. However, if, in addition to increased work, there is either ischemia caused by coronary thrombosis or anemia, or extensive myocardial disease as a result of infection, the heart will enlarge greatly.

Nature performs that experiment very well for us. One should remember that, in mitral stenosis, even when an acute rheumatic infection is present, the left ventricle, despite the fact that it is affected, will usually be small, whereas the left auricle and right ventricle, and even the right auricle, will be large. Therefore, we have an experiment in nature, in which, with a diseased heart, that part of the heart which has less work to do will not enlarge as much as the part that has more work to do.

In a group of cases of so-called idiopathic hypertrophy of the heart, which I described a number of years ago, evidence of myocardial disease was found invariably. We can assume clinically, and from our pathologic experience, that enlargement of the heart, even in a case of hypertension, means more than just increased work. It indicates either lack of circulation, or myocardial disease caused by infection or coronary disease.

DR. HELEN B. TAUSSIG, Baltimore.—We agree with Dr. Kugel that an increased load upon the heart causes enlargement. This is in accord with Sir Thomas Lewis's studies, which show that it is not the constant load, but an increased amount of work and increased strain, which causes cardiac enlargement. The heart

readily adjusts itself to the residual valvular lesions. I don't mean to say that there is no enlargement, but the enlargement caused by valvular damage is surprisingly slight.

Our studies are also in accord with Dr. Duckett Jones's observations concerning the regression of physical signs and the amount of improvement which may occur in cases of rheumatic fever and rheumatic heart disease.

In conclusion, let me repeat that we feel that severe, active infection is the cause of damage, and, further, that increasing the strain upon the heart when an active infection is present is making matters very much worse. For that reason we urge absolute rest in bed throughout the period of active infection.

METASTATIC BRONCHIOGENIC CARCINOMA OF THE HEART

Report of Case, With Clinical Diagnosis by Progressive Electrocardiographic Changes, and Pathologic Confirmation

James R. Reuling, M.D., Bayside, N. Y., and Louis Razinsky, M.D., Far Rockaway, N. Y.

MOST of the tumors of the heart and pericardium are asymptomatic and are, therefore, of interest only to the pathologist. Some, however, are the cause of cardiac dysfunction and present clinical features pointing to such involvement. A review of the clinical histories of these cases shows that neoplasm might be suspected if the clinician bears this possibility in mind.

In a comprehensive review of the literature, Yater,[1] in 1931, published numerous autopsy series that have been investigated in regard to the occurrence of cardiac metastases, and he concluded that tumors of the heart and pericardium are rare. More recently, several additional series have been published, from which it would appear that they are more common than believed. Pollia and Gogol[2] found twenty-nine secondary tumors of the heart among 12,000 autopsies, 1,450 of which were malignant tumors, an incidence of 2 per cent invasion in cases of malignancy. In a study of 327 autopsies on patients with known malignancy, Burke[3] found fourteen cases of metastatic involvement of the heart, constituting approximately 4.3 per cent of routine autopsies made in such cases at the State Institute for the Study of Malignant Disease, New York. Finally, the highest incidence yet published was found by Scott and Garvin[4] at the Cleveland City Hospital. Among 1,082 cases of malignant disease appearing in their series of 11,000 consecutive postmortem examinations, these authors found the heart, the parietal pericardium, or both, involved in 118 cases, an incidence of 10.9 per cent invasion in cases of malignancy.

Metastases to the heart have occurred from neoplasms of all the main organs. Scott and Garvin[4] found that carcinoma of the bronchus and of the breast is of paramount importance as a source of secondary tumors of the heart and pericardium, the incidence of involvement being 35.6 per cent in both instances. The mechanism of implantation of tumor tissue in the heart must vary considerably in individual cases. Most of them are associated with primary or secondary intrathoracic tumors, from which the tumor cells may gain access to the left side of the heart through the pulmonary veins and thence to the coronary arteries and the cardiac muscles. In the less common cases of implantation on

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the endocardium of the right side of the heart, the tumor cells probably gain entrance to the blood stream from the lymphatic duct and pass to the superior vena cava via the bronchial or azygos veins. Where the lymph nodes in close proximity to the heart itself are involved, as in the case of the tracheobronchial lymph nodes which drain the pericardium as well as the pleura, retrograde conduction along the lymphatic channels would allow a direct growth of the tumor cells backward to the heart muscle. In all cases of direct extension, the lymphatics may or may not play an important role.

The clinical features of neoplastic involvement of the heart have been well classified by Yater.[1] He groups these cases logically into those in which the clinical type is not suggestive of tumors of the heart and those in which the type is suggestive of such a diagnosis. Under the first type are those in which there is sudden death, terminal cardiac embarrassment, symptoms of congestive heart failure, or symptoms suggestive of subacute bacterial endocarditis. In the second group there are various abnormalities of rhythm, symptoms of congestive heart failure which develop without apparent cause in a patient with a known malignant process, accumulation of hemorrhagic fluid in the pericardial sac,[1, 5-7] and lastly, suggestive roentgenologic signs.[8] Frequently, a murmur which is believed to be typical of mitral stenosis is found.[8-10] This is often due to a pedunculated tumor of the right or left auricle, causing a functional stenosis of the tricuspid or mitral orifice with certain changes in position. It is also in these cases that sudden death occurs.

In patients with known malignancy, the sudden appearance of paroxysmal auricular tachycardia or paroxysmal auricular fibrillation or flutter[4, 11] is suggestive of cardiac tumor with involvement of the atria. The most common type of cardiac abnormality, however, has been associated involvement of some portion of the conduction system. These patients have shown bundle branch block.[1, 7, 12] Frequently, various degrees of A-V block,[13] and even complete A-V dissociation[1, 5] with the Stokes-Adams syndrome, have been found.

Barnes and associates[5] conclude that "on the basis of published tracings and on theoretical grounds, it is to be anticipated that most of the electrocardiographic changes that will be observed in cases of tumor of the heart will result from neoplastic invasion of the ventricles. It is probable that invasion of the conducting system will account for a majority of the abnormal electrocardiograms. Because of the more frequent invasion by tumors of the right ventricle than of the left,[11, 12, 14] right bundle branch defects should exceed those of the left bundle branch. Invasion of the muscle of the left ventricle without involvement of the bundle branches or of the pericardium should produce tracings closely similar to those obtained in the fibrotic stage following acute myocardial infarction (case of Siegel and Young[15]). Invasion of

the epicardium,[6] either alone or in conjunction with involvement of the ventricles, may produce or modify changes in the waves. If a patient, known to have had a neoplasm, more or less suddenly exhibits these electrocardiographic changes in the absence of any other pathological processes in the heart to explain them, then they contribute important presumptive evidence that the malignant process has invaded the heart."

A search of the literature reveals only eight cases of secondary tumors of the heart diagnosed during life,[4, 8, 11, 12] and to this group is added the case herein presented.

CASE REPORT

B. McC., a 63-year-old white male, was admitted to the Medical Service of the Queens General Hospital on Aug. 7, 1939, complaining of pain in the left anterior chest.

The past history included pneumonia many years previously and an admission to the genitourinary service of this hospital on March 20, 1939, for suprapubic prostatectomy. During the latter admission, roentgenologic examination of the chest on March 27, 1939 (Fig. 1), revealed no marked or unusual findings except increased hilar markings, and an electrocardiogram on March 21, 1939 (Fig. 6), showed regular sinus rhythm and vertical axis deviation.

The patient was discharged from the hospital on May 18, 1939. On June 22, 1939, he came to the outpatient department complaining of nonproductive cough, associated with pain in the left upper chest and back, and increasing dyspnea and wheezing (asthmatoid breathing), which had appeared one week following his discharge from the hospital. Examination revealed some dullness and diminished breath sounds in the left upper chest posteriorly. A roentgenologic examination on the same day (Fig. 2) disclosed no change from the findings of the previous examination.

At the time of his admission on Aug. 7, 1939, the patient gave a history that one week prior he had developed severe pain in the left chest anteriorly, constricting in nature and radiating to the left axilla. He stated that the pain was relieved after one hour by the application of a mustard plaster. He applied at the outpatient department, where examination showed a marked irregularity of the heart (auricular fibrillation), and he was admitted to the medical ward with a diagnosis of possible coronary occlusion. Examination several hours later revealed wheezing respirations, more marked on the left side; the heart was not enlarged; there was regular sinus rhythm, and the blood pressure was 100/60.

A roentgenologic examination of the chest on Aug. 14, 1939 (Fig. 3), disclosed considerable increase in the left hilar markings as compared with the previous films. The heart and aorta were normal as to size, shape, and position.

An electrocardiogram on Aug. 10, 1931 (Fig. 7), revealed regular sinus rhythm, with the QRS low and notched, and diphasic T and Q waves present in Lead III. On Aug. 14, 1939, fibrillation was noted again, and the impression arose that the initial onset of pain one week before admission might be explained on the basis of a paroxysmal auricular fibrillation. Digitalis and quinidine therapy was instituted, with marked subjective improvement, and the patient was allowed up and around the ward.

Another roentgenologic examination of the chest on Aug. 21, 1939 (Fig. 4), showed the peribronchial thickening of the left hilar region to be more marked than at any time since March 27, 1939, and the possibility of fibrotic tuberculous infiltration of the upper lobe of the left lung was suggested. The heart and aorta were normal.

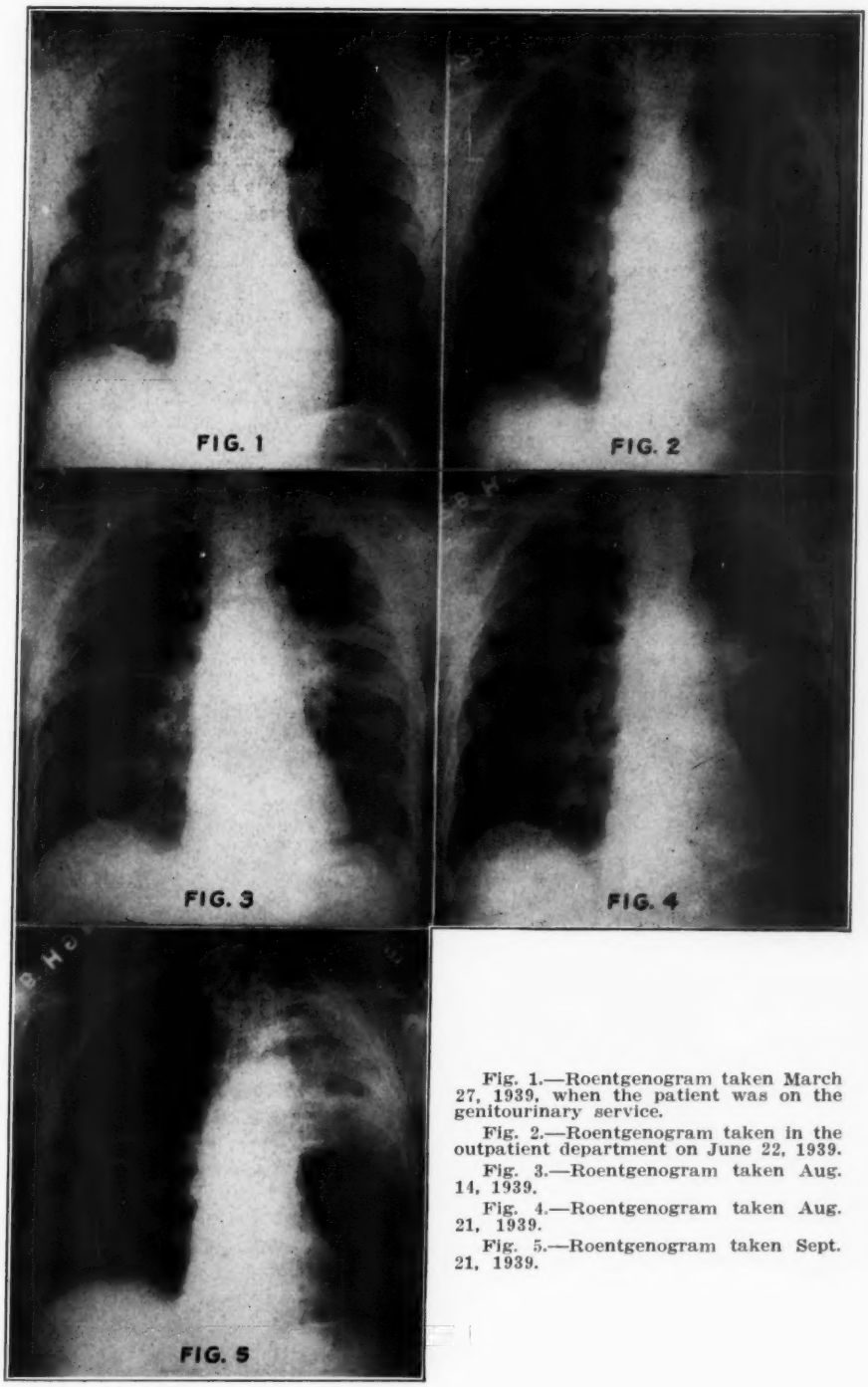

Fig. 1.—Roentgenogram taken March 27, 1939, when the patient was on the genitourinary service.

Fig. 2.—Roentgenogram taken in the outpatient department on June 22, 1939.

Fig. 3.—Roentgenogram taken Aug. 14, 1939.

Fig. 4.—Roentgenogram taken Aug. 21, 1939.

Fig. 5.—Roentgenogram taken Sept. 21, 1939.

On Aug. 29, 1939, the patient again developed cough and pain in the left anterior chest, and for the first time there was a temperature of 100.6° F. On the following day the temperature rose to 102.4° F., and examination again revealed dullness and diminished breath sounds over the upper lobe of the left lung posteriorly. From this time to the day of death there were daily fluctuations of temperature up to 103° F. On Sept. 1, 1939, the cough was accompanied by bloodstreaked sputum, and for the first time, a high-pitched, "sea-gull," systolic murmur was heard at the apex of the heart, associated with a thrill. On this day another electrocardiogram, which had been taken on Aug. 28, 1939 (Fig. 8), was reported and showed incomplete

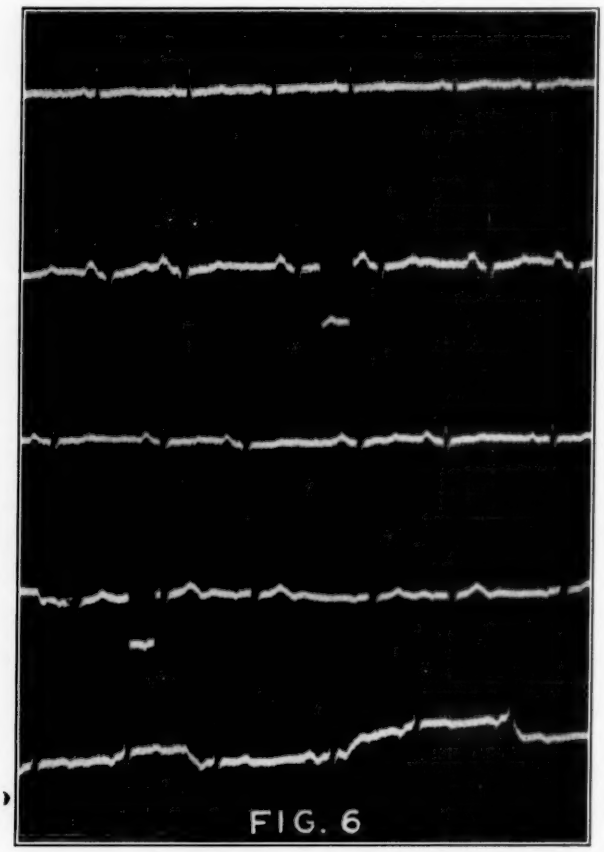

Fig. 6.—Electrocardiogram taken March 21, 1939, when the patient was on the genitourinary service.

left bundle branch block, with the QRS complexes slurred and widened (0.14 sec.) and with S-T depression and upright T waves in all standard leads. At this time, in view of the electrocardiographic changes, it was thought that there might have been a coronary occlusion at the onset, with involvement and possible perforation of the interventricular septum (thus accounting for the peculiar murmur), with the lung signs secondary to pulmonary infarction. However, the cough, the bloodstreaked sputum, the fever, and the physical findings persisted far beyond the usual expected period for such conditions; consequently, another roentgenologic examination of the chest was done on Sept. 21, 1939 (Fig. 5), and this revealed marked in-

creased density in the upper third of the left lung field, with atelectasis, displacement of the mediastinum to the left, and contraction of the left upper thorax. A cavity was also noted at the level of the second intercostal space, in the midclavicular line.

A review of the clinical course, in view of these findings, revealed that from the onset this case must have been one of bronchiogenic carcinoma of the left upper lobe bronchus, and that the cardiac signs could now be best explained as metastatic involvement of the conduction system of the left ventricle. Soon, recurrent attacks of complete heart block occurred and, together with the peculiar murmur heard, presented presumptive evidence of neoplastic involvement of the interventricular septum. Finally, the complete heart block became persistent (electrocardiogram on Oct. 16, 1939 (Fig. 9). On the day prior to death there occurred two typical attacks of Stokes-Adams syndrome. The patient died suddenly on Oct. 23, 1939.

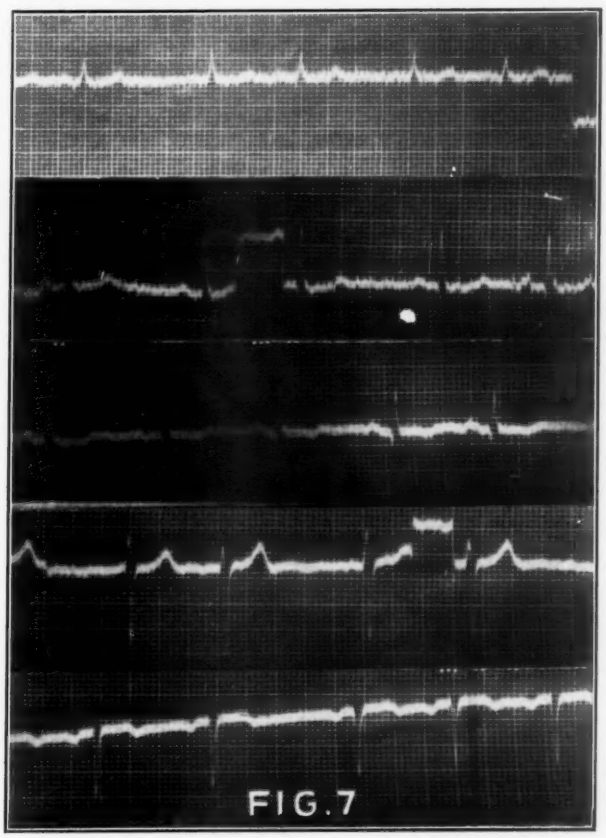

Fig. 7.—Electrocardiogram taken Aug. 10, 1939.

The clinical diagnosis was: (1) bronchiogenic carcinoma of the left upper lobe bronchus, with abscess cavitation; (2) metastasis to the heart, particularly involving the interventricular septum.

POST-MORTEM FINDINGS*

The left pleural cavity contained about 1,000 c.c. of clear, straw-colored fluid. The left lung was firmly adherent to the parietal chest wall. The left upper lobe was

*Abstract of post-mortem examination performed by Dr. Nathan Mitchell.

occupied by a large mass. The bronchi were traced, and in the region of the left upper lobe bronchus, whitish, firm, opaque tissue, with ulceration of the mucosa, was noted. This tissue extended upward along the course of the left main bronchus, involving the peribronchial and paratracheal tissues. The bronchus was traced upward and it led into a multilocular cavity which contained several ounces of thick, yellowish, creamy pus. Surrounding this cavity and extending into the left lower lobe, diffuse, uniform consolidation of the parenchyma was noted.

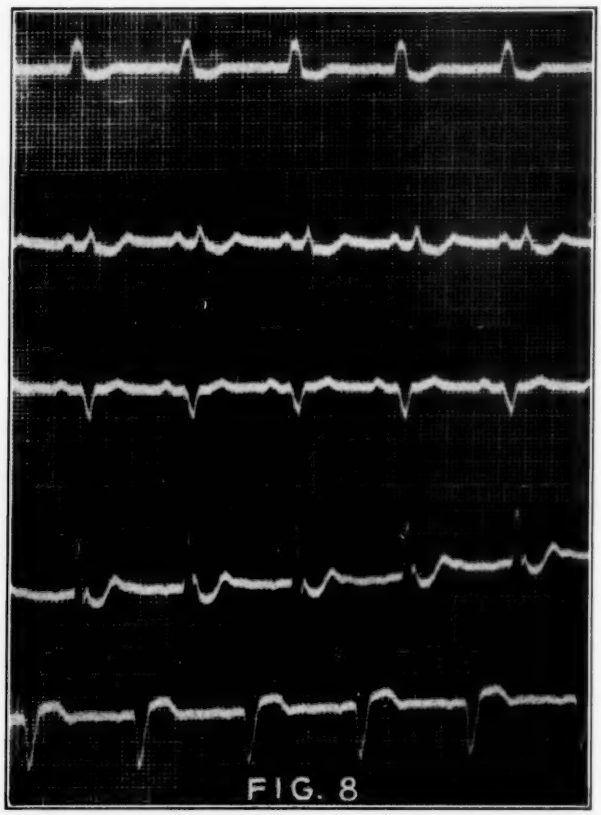

Fig. 8.—Electrocardiogram taken Aug. 28, 1939.

The heart was moderately enlarged. Several white, firm nodules could be seen projecting through the pericardium. On section of the heart, whitish, nodular areas could be seen scattered throughout the myocardium (Fig. 11). These nodules varied from 1 to 4 cm. in diameter and were located in the left ventricular wall and the interventricular septum. There was one large nodule occupying the base of the interventricular septum, extending from the endocardium of the left ventricle through to the endocardium of the right ventricle (Fig. 10), the entire mass being located beneath the right coronary cusp of the aortic valve. The papillary muscles were likewise invaded by the same whitish tissue. The pulmonary arteries and veins were constricted, and the intima was folded by thrombotic, whitish material. The mediastinal lymph nodes were not involved.

The terminal ileum contained a small, hard nodule measuring 3 mm. in diameter. A whitish nodule measuring 1 cm. was seen in the upper pole of the right kidney.

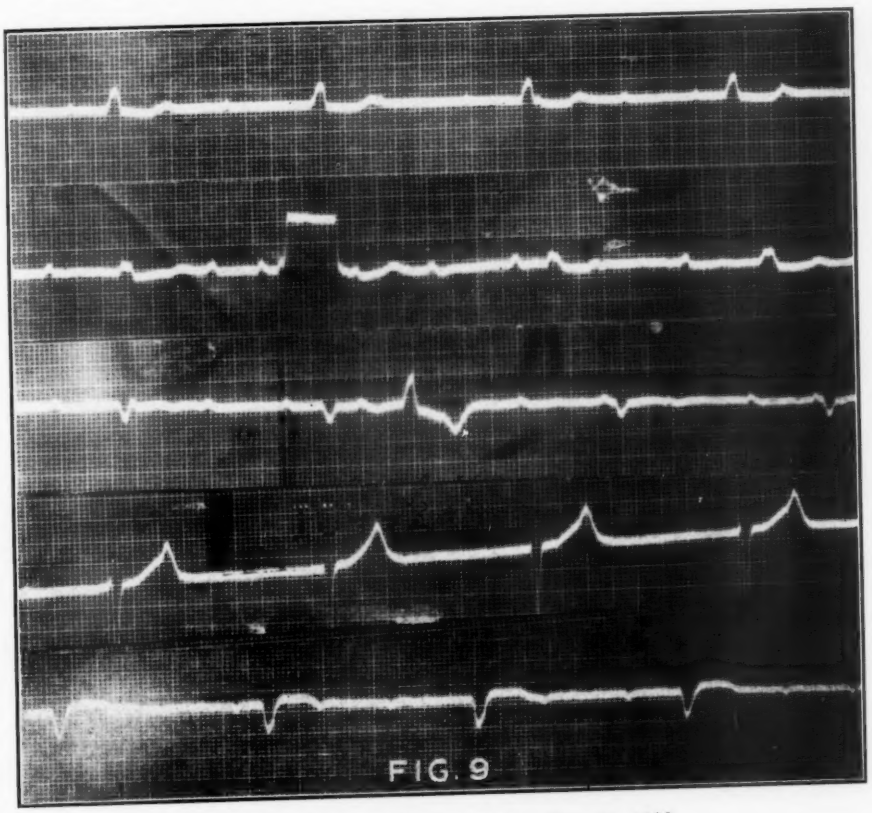

Fig. 9.—Electrocardiogram taken Oct. 16, 1939.

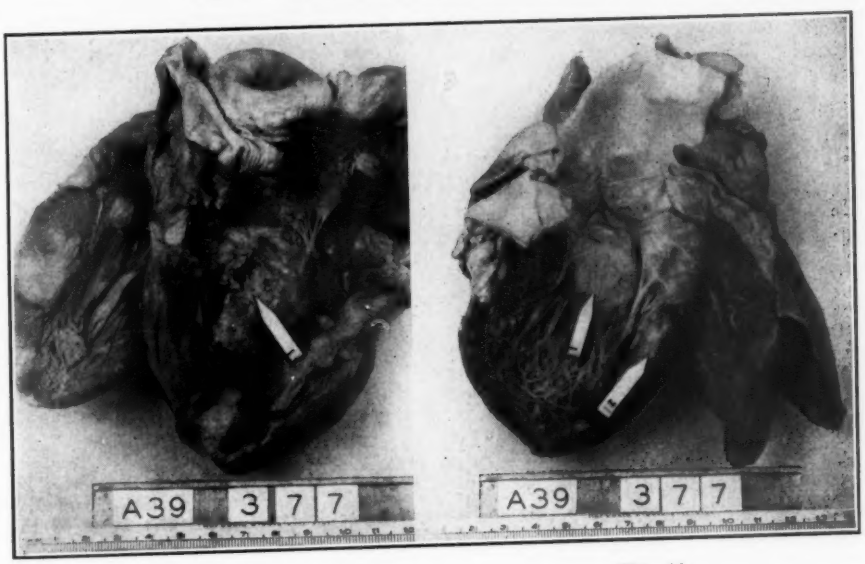

Fig. 10.

Fig. 11.

Near the center of the left kidney, there was a broad, depressed, yellowish, pyramidal-shaped area, well demarcated from the surrounding tissue. The neck of the bladder and the prostatic urethra revealed distortions of the mucosa, and on cut section, the prostate showed many opaque, nodular areas.

Fig. 12.

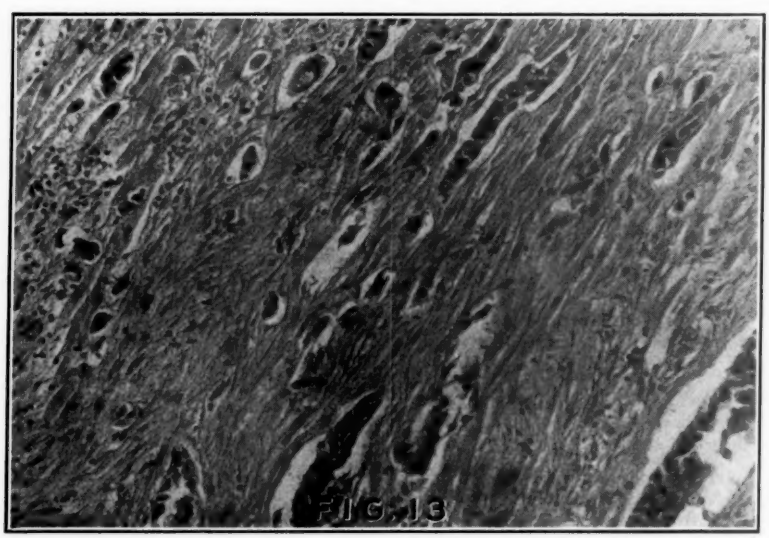

Fig. 13.

Microscopic study disclosed a primary squamous-cell carcinoma with keratinization and necrosis, and deep invasion of the bronchial wall, with ulceration of the mucosa. Lymphatic channel and lymph node invasion and invasion of the pulmonary vessels with tumor thrombosis were found (Fig. 12). Other areas of the lung revealed definite metastatic invasion with permeation of lymphatics and of the alveolar

spaces. The cavity in the left upper lobe showed tumor tissue in its wall and regional chronic pneumonitis. The heart revealed extensive invasion by squamous-cell carcinoma, including tumor thrombi in some of the coronary veins (Fig. 13). The entire region of the base of the interventricular septum, involving the bundle of His and both the right and left branches, disclosed extensive invasion and destruction. The kidney showed an isolated metastatic nodule. The aorta showed limited syphilitic aortitis. The ileum disclosed a small leiomyoma separating the muscle layer and elevating the serosa. The prostate revealed a small, miniature adenocarcinoma, with both chronic and acute prostatitis evident.

COMMENT

Most cases of metastatic carcinoma of the heart are associated with primary or secondary intrathoracic tumors. Thus, in Lynburner's series,[14] 88 per cent of the tumors were intrathoracic, and 72 per cent involved the lung. In view of its high incidence, bronchiogenic carcinoma would be of paramount importance in showing a relatively common tendency to invade the heart. This is borne out by the statistics of Scott and Garvin,[4] as previously mentioned.

The case reported herein is of interest for several reasons: In the first place, it afforded a study of the complete clinical course of bronchiogenic carcinoma; and in the second place, it was marked by the presence, during some part of its course, of nearly all of the more common cardiac abnormalities of neoplastic involvement of the heart reported in the literature. Thus, the onset of cardiac symptoms was marked by paroxysmal auricular fibrillation, followed by left bundle branch block and, finally, by complete A-V dissociation with a Stokes-Adams syndrome. These changes in a patient suspected of having malignancy of the lung, in the absence of any other pathologic processes in the heart to explain them, offered important presumptive evidence that the malignant process had invaded that organ. Finally, an opportunity was afforded to check in the human being the clinical findings of conduction system defects with post-mortem findings. It was of interest to determine whether the electrocardiographic finding of left bundle branch block was associated with neoplastic destruction of the left bundle branch, and whether the complete heart block was due to involvement of the bundle of His alone or to simultaneous involvement of both main branches. Unfortunately, post-mortem examination revealed complete destruction of the bundle and its branches, thus rendering impossible morphologic correlation of primary left bundle branch involvement with extension to the right branch during invasion of the entire bundle, as the cause of the complete heart block.

SUMMARY

Although metastatic tumors of the heart and pericardium are considered rare, recent studies of autopsy series reported in the literature make it appear that they occur more commonly than is ordinarily believed.

Carcinoma of the bronchus is of paramount importance as a source of secondary tumors of the heart and pericardium.

The clinical features suggestive of a diagnosis of metastatic tumors of the heart are various abnormalities of rhythm, such as heart block, congestive failure, or hemorrhagic or serosanguineous pericardial effusion, each suddenly developing without apparent cause in a patient with known malignancy.

A case of bronchiogenic carcinoma with metastasis to the heart, diagnosed during life, is presented to augment the small group of cases already reported in the literature.

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CIRCULATORY EFFECTS FOLLOWING THE INTRAVENOUS ADMINISTRATION OF PITRESSIN IN NORMAL PERSONS AND IN PATIENTS WITH HYPERTENSION AND ANGINA PECTORIS

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THIS report deals with some of the cardiovascular reactions observed during the administration of posterior pituitary extract to nine normal persons, to four patients with essential hypertension, and to two with angina pectoris. Previous studies have been concerned chiefly with the effects of large single doses given subcutaneously or intramuscularly. In the present study, pitressin was given intravenously over relatively long periods of time, and the circulatory effects observed suggested certain clinical possibilities.

METHOD

Pitressin* (1 c.c. = 20 I. U.) was diluted with normal saline to provide a concentration of 1:1,000, and the rate of flow, during the administration, was controlled and measured by means of an especially prepared burette. Save in the earlier tests, a second burette containing normal saline was included in the circuit in such a manner that a change in flow from saline to pitressin, or vice versa, could be made readily. In most instances, 0.1 c.c./Kg./min. of the pitressin solution was given over a period of from thirty minutes to one hour or more. If this was insufficient to produce severe abdominal cramps, the rate of flow was doubled or tripled. Blood pressures were measured with a mercury sphygmomanometer. Skin temperatures were determined by means of a Tycos dermatherm. Electrocardiograms were taken with the subject recumbent. Grollman's acetylene method was used in determining the cardiac output.

The person to be tested was allowed to lie quietly for at least thirty minutes while control observations were made in a room with nearly constant temperature. When these observations indicated that a stable state had been reached, the intravenous infusion of saline solution was begun. When the reactions incident to this procedure had disappeared, the change to pitressin solution was made by simply turning a stopcock. Notes were made on the changes in skin color, character of the pulse, and subjective symptoms during the course of the experiment.

THE EFFECTS: GENERAL CONSIDERATIONS

Almost immediately after the administration of pitressin was started, pallor of the skin and mucous membranes became apparent. The subject appeared ill but felt well. This discrepancy was very striking and sometimes almost unbelievable. The temperature of the skin fell very

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*Pitressin as prepared commercially by Parke, Davis & Co. was used throughout these experiments.

little during the test period, and, again, a sharp contrast was observed between color and warmth of the skin. The pulse rate did not change significantly, but the amplitude of the radial pulse grew much smaller and, in some subjects, the pulse became difficult to palpate. Despite this obvious arterial constriction, the alterations in blood pressure were small. As a rule, restlessness developed, followed by general malaise and weakness. Sweating always occurred toward the end of the test and was sometimes profuse, interfering with accurate skin temperature determinations.

Abdominal symptoms occurred in every instance, but with wide variations as to time and character of onset. The onset was heralded with nausea, a feeling of weight or a burning sensation in the epigastrium, and borborygmus. Cramplike pains in the lower abdomen usually were followed by bowel urgency; three subjects had a large evacuation immediately following the test.

SKIN COLOR

Pallor of the skin developed very rapidly following the injection of pitressin. Pallor was observed when the dilution of pitressin in the blood was calculated to be approximately 1:3,000,000. This is in keeping with the well-known fact that the active principles of the posterior portion of the pituitary gland act in minute doses, smaller than those of any known substance, except perhaps the protein poisons. Sacks[1] has shown this pallor to be the result of the action of posterior pituitary extract on the capillaries and subpapillary venous plexuses, which are the vessels chiefly responsible for skin color.

Affecting the more highly colored portions of the face first, the pallor gradually increased in intensity, involving the entire face, neck, ears, lips, and mucous membranes of the mouth. Later, pallor of the hands, arms, and other portions of the body was observed. The pallor persisted for one and one-half to two hours after the injection of pitressin was stopped.

It is important to point out the rapidity with which changes in skin color occurred as compared with changes in skin temperature. The former were almost immediate and were striking. The latter took place more slowly and were less definite. This adds further confirmation to the work of Sacks in showing that there is only a slight pressor effect, at least in the higher dilutions of pitressin, on the vessels responsible for the warmth of the skin.

SKIN TEMPERATURE

Skin temperature determinations were made in sixteen experiments on thirteen subjects. The areas most commonly tested were the forehead and left hypothenar eminence. The usual precautions were observed in so far as possible, but in many tests some factor was present

which vitiated the results. In four tests the conditions were ideal, but the results did not differ significantly from the others. The reason for this probably rested in the fact that the duration of the experiment was rarely over two hours. In general, skin temperature fell slightly, about 1 to 2° F., during the course of the experiment. Exceptionally, the temperature rose a degree or remained at the control level. As emphasized above, even when the pallor was extreme, there was little change in skin temperature. This is in keeping with the observations of Krogh[2] and others who found that in high dilution posterior pituitary extracts have little effect on the size of the arterioles upon which skin temperature is mainly dependent.

BLOOD PRESSURE AND PULSE RATE

Oliver and Schafer,[3] in 1895, observed a rise in blood pressure in anesthetized animals following the intravenous injection of extracts of the pituitary gland. A few years later Howell[4] proved that extracts of the posterior lobe of the gland are responsible for this pressor effect, and this extract became known as vasopressin. Since then, numerous investigators[5] have studied the pressor response of this hormone, both in animals and in man, but reports of its effect on blood pressure have been conflicting. The fact emerges that the blood pressure response

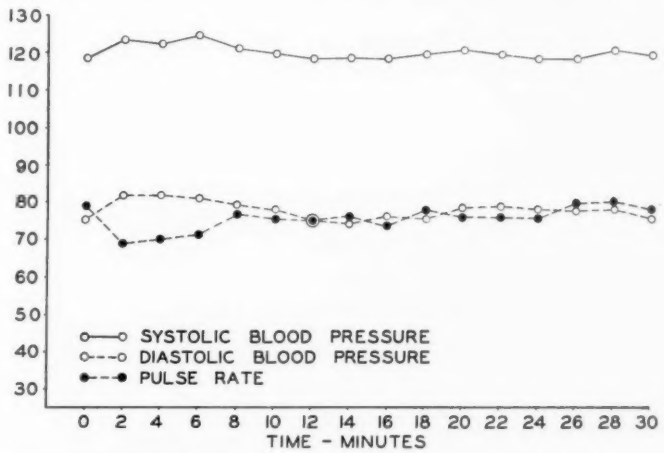

Fig. 1.—Average changes in blood pressure and pulse rate in nine normal persons during intravenous administration of pitressin.

depends on several variable factors, including the amount of the substance given, manner of administration, number of injections, and the presence of other drugs. From a review of published reports, it would appear that in man, moderate amounts of posterior pituitary extract usually do not cause marked changes in blood pressure. A certain tolerance may be established with repeated injections so that the blood pressure response becomes less marked.

Fig. 1 shows the average changes in blood pressure and pulse rate in nine normal persons during the intravenous administration of pitressin. It is readily seen that after a slight initial rise in systolic and diastolic blood pressure, and a slight fall in pulse rate, control values are quickly reached. These changes are probably significant even though slight, because a temporary rise in pressure was observed in each instance. Furthermore, the change from saline to pitressin was made without the subject's being aware of it, and the rise in blood pressure usually occurred before subjective symptoms were apparent. Slight temporary slowing of the pulse rate is probably due to the depressor effect resulting from the increase in blood pressure.

Four patients with essential hypertension were similarly tested, and blood pressure and pulse rate responses of similar magnitude were observed. The only difference was that in the hypertensive subjects, the return of the blood pressure toward the control level occurred more slowly. The changes observed in two patients with angina pectoris were insignificant, but the absence of any fall in blood pressure is of interest because it is thought by some that a fall in blood pressure following posterior pituitary extracts is the result of cardiac weakness resulting from constriction of the coronary vessels.

CARDIAC OUTPUT

There has been little study of the alteration in cardiac output in man following the injection of pituitary extracts. Grollman and Geiling[6] made a series of determinations at fifteen-minute intervals on two normal subjects after a single intramuscular injection of posterior pituitary extract. Immediately after administration, they found a slight decrease in cardiac output (average 12 per cent), followed by an increase, and then by a return to the initial level.

TABLE I

NO.	BEFORE PITRESSIN	DURING PITRESSIN	CHANGE IN METABOLIC RATE (%)	CHANGE IN CARDIAC OUTPUT (%)
1	5.11	4.82	-27	-5.1
2	5.92	5.35	-15	-9.6
3	5.03	5.15	-10	+2.4
4	6.08	5.75	-16	-5.0
5	6.43	5.99	± 0	-6.8
6	6.35	5.98	+ 3	-5.8
Average	5.82	5.50	-10.8	-5.0

In our experiments we followed Grollman's technique, except that basal conditions were not observed. The tests were performed in the afternoon; the subject was allowed a small luncheon, and the experiment was begun about one and one-half hours later. Although the food affected the absolute values of the cardiac output, the relative values

were valid because of the short duration of the experiment. Determinations were made just before and during the height of administration of pitressin.

Table I shows the results in the six cases tested. Cardiac output, on the average, was decreased 5.0 per cent. The large decreases in cardiac output observed in animal experiments have been thought by some observers to be due to a direct effect of the drug on the myocardium. In these experiments much larger doses were employed than in the present tests.

ELECTROCARDIOGRAMS

Electrocardiograms were taken of six normal subjects before administration of pitressin and at intervals during the administration. No significant changes were observed.

PITRESSIN AND ANGINA PECTORIS

The action of posterior pituitary extract on coronary vessels and on the heart is better known for animals than for man. Numerous investigators[7] have shown that this extract causes constriction of the coronary vessels and weakening of the heart in animals. It should be noted, however, that the doses used are usually much greater than the amount normally excreted. It is assumed that posterior pituitary extracts cause constriction of the coronary vessels in man. Kountz and Smith,[8] however, did not observe any significant alteration in coronary flow when pituitary solution was added to the perfusate of a revived dilated human heart. Goldenberg and Rothberger[9] conclude, from their experiments and from a survey of the pertinent literature, that the coronary constrictor action of pitressin provides a means of testing the "spasm theory" of angina pectoris. We thought it would be of interest, therefore, to give pitressin to patients with angina pectoris.

Two patients who had easily provoked anginal pain were selected for testing. Both experienced pain on very small effort or excitement and occasionally even while resting in bed. The tests were carried out in the usual manner, except that the rate of injection of the pitressin was increased more cautiously.

The readings and notes given in abbreviated form in Table II were made while testing Mr. G., a cook, 56 years of age.

After a suitable control period, physiologic saline solution was allowed to run into a vein. The unpleasantness and excitement incident to the introduction of the needle were sufficient to provoke slight but definite substernal discomfort. This quickly passed, and some time later the change was made from saline to pitressin without the subject's knowledge. The solution of pitressin was allowed to run until abdominal cramps became uncomfortable. Anginal pain was not

produced. This same patient on another occasion was given adrenaline, in a dilution of 1:1,000,000, intravenously. Pain resulted very quickly and was preceded only by a slight rise in blood pressure and pulse rate.

TABLE II

TIME	PITRESSIN (C.C./KG./MIN.)	BLOOD PRESSURE		PULSE RATE	REMARKS
		SYSTOLIC	DIASTOLIC		
2.16	0	140	92	88	Comfortable
2.40	0	140	90	84	
2.56	0	142	90	88	
2.57					Injection of saline begun
2.58	0	160	100	100	
3.00	0	158	110	100	Slight substernal pain
3.02	0	148	90	96	Pain less
3.04	0	140	92	96	Pain gone
3.12	0	136	90	86	
3.24	0	132	88	86	
3.28	0	132	90	84	
3.30					Injection of pitressin begun
3.32	0.02	134	90	88	Beginning pallor
3.42	0.02	136	86	80	Pallor marked
3.52	0.04	134	90	80	
4.02	0.10	138	88	78	
4.12	0.12	138	84	80	Cramps
4.18	0.12	138	86	82	Complained of abdominal cramps
4.22	0.12	134	84	80	
4.24					Pitressin solution stopped

TABLE III

TIME	PITRESSIN (C.C./KG./MIN.)	BLOOD PRESSURE		PULSE RATE	REMARKS
		SYSTOLIC	DIASTOLIC		
2.00	0	120	65	68	Face a ruddy color
2.05	0	115	65	68	
2.13	0	115	70	68	
2.20					Saline solution started
2.22	0	112	70	68	
2.27	0	110	65	64	
2.30					Saline stopped; pitressin started
2.32	0.06				Slight pallor
2.34	0.06	120	72	60	Moderate pallor
2.42	0.06	114	72	60	
2.52	0.12				Rate of injection increased
2.55	0.12	118	70	64	Slight abdominal distress; slight sweating; pallor marked
3.04	0.12	112	70	64	Abdominal cramps moderately severe
3.06					Pitressin stopped

A similar test was carried out on Mr. H.,* aged 58 years, and anginal pain did not occur although sufficient pitressin was given to provoke well-marked abdominal cramps. The notes on the case are given in Table III.

*This patient has since died, and autopsy revealed an extreme degree of coronary arteriosclerosis.

The above results would seem to point to a curious paradox, in that pitressin, a drug known to cause coronary vasoconstriction, did not provoke pain in anginal patients, while adrenaline, a drug known to cause coronary vasodilatation, readily provoked pain. These facts require explanation. It would appear either that coronary vasoconstriction was not produced with pitressin, or, if it was, that there must have been at least a corresponding decrease in the work of the heart. Experimental evidence points to the fact that pitressin actually does constrict the coronary vessels to a marked degree. Our results show that both the cardiac output is slightly decreased and the metabolic rate is lowered by an average of 10.8 per cent. Accordingly, it would seem that the decrease in coronary flow was compensated for by the decrease in the work of the heart. An interesting parallel is seen in the case of adrenaline. This drug may quickly provoke pain in anginal patients although it causes coronary vasodilation. The explanation lies in the fact that the work of the heart is increased to a greater extent than is the coronary flow.

Katz and Lindner[10] point out that "for practical purposes the important thing is not whether the substance has a coronary vasodilator or vasoconstrictor action nor whether the substance increases coronary flow or decreases it but rather how it influences the relation of the change in coronary flow to the alteration in the work of the heart and to the energy cost on the part of the heart doing this work." On this basis, we may conclude, therefore, that pitressin in amounts sufficient to provoke distressing abdominal cramps does not significantly decrease the blood supply to the myocardium in relation to the work of the heart and that it is safe and practical to give pitressin to patients with coronary heart disease.

DISCUSSION

It is clearly apparent from these results that pitressin, given in the manner described above, has a cumulative effect in that a point of tolerance is reached. The limiting symptoms are related to the gastrointestinal tract, and these may be pronounced if enough of the drug is given. These symptoms include nausea, vomiting, and abdominal cramps, sometimes followed by evacuation of the bowel. There was not a single instance of significant cardiovascular symptoms in either normal persons or cardiac patients. There was evidence of constriction of the minute vessels and capillaries of the skin and of the large arteries; there was little effect on the arterioles, judging by the minor alterations in blood pressure and skin temperature. Furthermore, there was no evidence that the heart was adversely affected. The cardiac output was slightly decreased, and the metabolic rate was lowered. Pain was not produced in patients with severe coronary arteriosclerosis who were subject to easily induced attacks of angina pectoris.

In contrast to the above, severe symptoms have been reported following large single injections of posterior pituitary extract. These include cyanosis, shallow respirations, sweating, palpitation, faintness, feeling of heat, and abdominal cramps. Sometimes these symptoms are severe and alarming, and convulsions have been observed. These symptoms may be accompanied by considerable rises in blood pressure and other evidence of vasoconstriction. For these reasons and because of the known coronary vasoconstrictor action in animals, there has been a natural hesitancy to use posterior pituitary extracts in certain patients, especially those with heart disease.

Our experience suggests that pitressin may be slowly injected intravenously in amounts sufficient to produce marked gastrointestinal symptoms without producing alarming or even significant circulatory symptoms. This is true for normal persons and for patients with hypertensive or coronary heart disease. By the same technique it is possible that in pregnancy or in the treatment of ileus the desired therapeutic effect could be produced without fear of untoward circulatory symptoms.

SUMMARY AND CONCLUSIONS

A dilute solution of pitressin given by intravenous infusion has a cumulative effect.

Nine normal persons, four patients with essential hypertension, and two patients with coronary heart disease were given a dilute solution of pitressin intravenously over a period of from thirty minutes to one hour or more.

Gradually developing gastrointestinal symptoms limited the amount which could be given.

Significant cardiovascular symptoms were observed neither in the normal persons nor in the patients with heart disease. There was evidence of marked constriction of the minute vessels and of the large arteries, but not of the arterioles. There were only slight changes in the pulse rate, blood pressure, metabolic rate, and cardiac output.

Anginal pain was not reproduced in two patients with severe coronary heart disease who received sufficient pitressin to cause uncomfortable abdominal cramps. A minute amount of adrenaline when given to one of these patients produced anginal pain. It is suggested that in certain respects pitressin and adrenaline act in an opposite manner; the former causes coronary vasoconstriction but a decrease in the work of the heart, while the latter causes coronary vasodilation but an increase in the work of the heart.

Following the procedure used in these tests, pitressin, in therapeutic amounts, may be given without fear of untoward cardiovascular effects.

We should like to express our thanks to Dr. Paul D. White, in whose laboratory this work was carried out, for his interest and advice.

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EFFECT OF SHORT-WAVE DIATHERMY ON THE CUTANEOUS TEMPERATURES OF THE FEET

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THE primary value of heat in the treatment of peripheral vascular disease lies in its ability to produce peripheral vasodilation.[1] However, local heat is capable of doing more harm than good.[1-3] It is known that short-wave diathermy causes more or less deep through-and-through heating of the bodily region to which it is applied, and is thus more efficient than the ordinary methods of heating by conduction or infrared irradiation. However, it is our opinion that, when arterial insufficiency is present, local application of short-wave diathermy is contraindicated fully as much as is any other form of local application of heat, and that the contraindications far outweigh any advantages the method might have.

The contraindications to the employment of heat locally, plus recognition of the fact that the primary value of heat lies in its ability to cause vasodilation, suggest the advisability of inducing peripheral vasodilation by the application of heat over remote regions of the body which are unaffected by the lesions of peripheral vascular disease. That general peripheral vasodilation may follow application of heat to a region remote from the affected extremity has been demonstrated by many investigators.[4-10] Because of the deep through-and-through heating of a region of the body when short-wave diathermy is used, this method should be ideally adapted to produce peripheral vasodilation by remote heating of the tissues. It is realized that temperatures of the skin may not indicate the temperatures of the deeper tissues, but such temperatures are thought to indicate, at least, the arteriolar activity of the skin, so important in peripheral vascular disease.[11]

Without discussing the many controversial reports regarding so-called specific effects of short-wave diathermy on the peripheral capillaries, we believe that no conclusive experiments have been brought forward to indicate the existence of any such specific effect, whether it be vasoconstricting or vasodilating. We are inclined to agree with Weisz and associates,[12] who, after scientific experimental work, found no effect of short-wave diathermy on the capillaries of a frog's tongue which could not be explained on a purely thermal basis. One of us (Krusen[13]), in a

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survey of the literature, found that in the light of knowledge in the field of short-wave diathermy then existing, the effects could be explained only on the basis of the heating which was produced.

TECHNIQUE

The apparatus for measuring the skin temperature which we used in the following observations was the cutaneous thermocouple described by Eddy and Taylor.[14] The continuous application of multiple thermocouples was tried, but it was found that short-wave current, even so remotely applied, caused the thermocouples to heat beyond the actual temperature of the skin. Therefore, the portable cutaneous thermocouple was used, and all readings were recorded with the diathermy current turned off. It was found that maximal temperature of the skin was not indicated by the thermocouple until after the current had been turned off for one-half to one minute; that is, the temperature indicated by the thermocouple applied immediately after the current was turned off was from 0.5 to 1.5° C. lower than the temperature indicated when the thermocouple was applied from thirty seconds to one minute later. No scientific explanation of this phenomenon can be offered at present. No such delay in maximal reading was noted following other methods of warming the body.

The observations which we made were carried on in a room in which the temperature was manually controlled. This room could easily be maintained at a constant temperature for the three hours required to conduct each observation. The temperature of the air in the room was most frequently kept at 78° F. (25.5° C.), although occasionally it was maintained at 74 or 76° F. (23.3 or 24.2° C.). Sheard and associates[15] found that this range of temperature is somewhat below the environmental temperature at which the peripheral vessels dilate, and thus permits proper evaluation of the various methods of vasodilation used. Another equally important reason for maintaining a range of temperature of 74 to 78° F. (23.3 to 25.5° C.) is that many of the subjects employed were rather debilitated persons who would have been uncomfortable in the supine position with only a sheet or turkish towel over the chest, trunk, and thighs, at a temperature below this range.

An attempt was made to stabilize the temperatures of the skin of the extremities by withholding the meal prior to each observation. To this end, the subject lay supine with feet, head, and arms uncovered, in a room maintained at constant temperature for one-half to one hour, or until three consecutive readings of the skin temperature over the plantar surface of the first and third toes and over the dorsum of each foot had been recorded.

Various applications of short-wave diathermy suggested themselves, and the following methods were tried:

1. Four turns of diathermy cable were wrapped around the thigh of the normal, or the less severely involved, extremity.
2. This same application was made over the thigh of the involved limb.

3. The cable was applied over the lower portion of the abdomen in the form of an involute coil of four turns (a so-called pancake coil).

4. The cable in this same "pancake" form was placed under the lumbosacral region of the subject.

5. The pad and cuff technique was employed. A pad measuring 4 by 6 inches (10 by 15 cm.) was placed under the lumbosacral region, and a cuff measuring 3 by 12 inches (8 by 30 cm.) was applied around the middle third of the normal or less severely involved limb.

6. The same method as that last mentioned (5) was employed, except that the cuff was applied around the involved limb.

7. Pads measuring 4 by 6 inches (10 by 15 cm.) were applied for through-and-through treatment of the lower abdomen. That is, one pad was placed over the lower portion of the abdomen and the other one was placed under the lumbosacral region.

In all the above applications, the electrodes used were spaced at least 1 inch (2.5 cm.) from the skin by turkish toweling. This was done so that a maximal deep heating of tissue with minimal heating of the skin would be obtained. It is a well-known fact, demonstrated on living tissue by various investigators, that the greater the distance of spacing between the skin and the electrode, the more uniform is the deep heating of tissue.[12, 13]

After using the various applications previously mentioned and comparing one with the other, several points became evident. So far as the degree of resultant vasodilation which was produced is concerned, all the methods appeared to be suitable and their effects were comparable. In this regard, no one method seemed to have any advantage over others. However, in the matter of technique of application and comfort of the patient, several methods had rather marked disadvantages. It is a tedious procedure to apply the cable around the thigh, and rarely can this application be left during the entire hour of heating without the development of "hot spots." These chiefly occur where the weight of the limb exerts pressure on the turns of cable passing under it.

For those not fully acquainted with the application of short-wave diathermy, it is to be noted that a mechanical means of determining the exact amount of short-wave radiation introduced into the patient is not available at the present time, so that it is necessary to rely entirely on the subjects' sensation of "comfortable heat" for determination of dosage. Admittedly, this method of determining dosage is far from satisfactory, since personal interpretation of "comfortable heat" varies greatly. However, this disadvantage is common to all short-wave diathermy applications. It was minimized, so far as these studies were concerned, by using the same diathermy apparatus and identical applications on each patient. The approximate meter reading to be used can be determined best by employing a reliable assistant to act as a subject. This meter reading can be used on each patient with but small variation.

When it was ascertained that no one of the applications previously mentioned proved itself superior in its ability to promote peripheral

vasodilation, it was decided to use constantly that method which had presented the least technical difficulties. This was found to be the application of the cable in "pancake" formation under the lumbosacral region. This application was further modified by placing the cable under a mattress approximately 1½ inches (4 cm.) in thickness, similar in construction to the kapok or hair-filled, rubberized fabric-covered mattress used in the short-wave diathermy cabinets for induction of fever. This method proved highly satisfactory, since it provided nearly uniform application with a minimum of discomfort to the patients.

RESULTS OF OBSERVATIONS

Twenty observations (Table I) were made on eleven normal persons. In eighteen of these observations the temperature of the skin of the plantar surface of the right and left first toes increased to between 33.0 and 35.5° C. during one hour of irradiation with short-wave diathermy. In the remaining two observations, both of which concerned the same person, the temperature of the toes increased only to values between 28.0 and 30.5° C. The oral temperature varied from no change in one observation to an increase of 1.2° F. in two others.* The average change in all observations was an increase of 0.6° F. (0.33° C.).

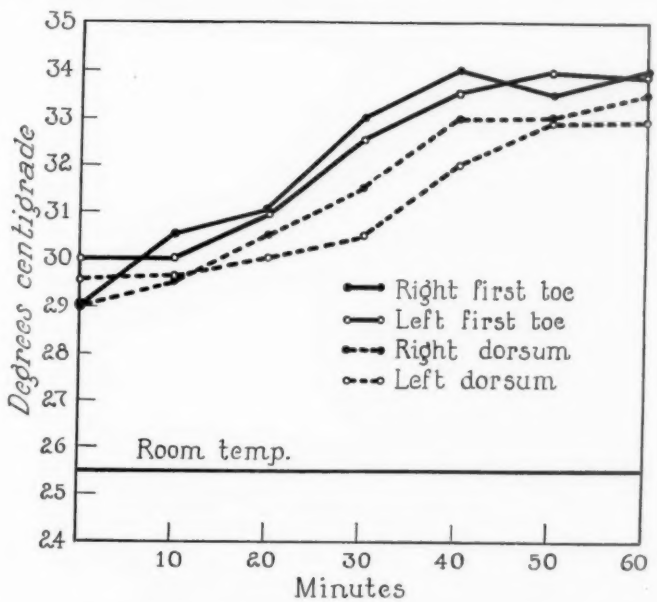

Fig. 1.—Changes in temperature occurring during observation 13 (Table I) on a normal subject, after sixty minutes of application of heat.

Fig. 1 (observation 13, Table I) shows the changes in temperature of the skin in a typical observation of this series. The temperature of the first toes increased to approximately 34.0° C. in about forty minutes,

*Because in this country physicians usually think of oral temperatures in terms of the Fahrenheit scale, the oral temperatures are recorded in Fahrenheit degrees rather than in centigrade degrees.

TABLE I

CHANGES IN TEMPERATURE IN THE SKIN OF THE TOES AND FEET, AND OF THE MOUTH: TWENTY OBSERVATIONS ON ELEVEN NORMAL SUBJECTS AFTER ONE HOUR OF SHORT-WAVE DIATHERMY

OBSERVATION	AGE (YR.) AND SEX OF PATIENT	MODE OF APPLICATION OF DIATHERMY	FIRST TOE, PLANTAR SURFACE (°C.)						DORSUM OF FOOT (°C.)						ORAL TEMPERATURE (°F.)			ROOM TEMPERATURE (°C.)
			RIGHT			LEFT			RIGHT			LEFT						
			AT REST	AFTER DIATHERMY	CHANGE	REST	AFTER DIATHERMY	CHANGE	REST	AFTER DIATHERMY	CHANGE	REST	AFTER DIATHERMY	CHANGE	REST	AFTER DIATHERMY	CHANGE	
1	36, M	Pads over and under abdomen	29.5	34.5	+5.0	29.0	35.0	+5.0	30.5	34.0	+3.5	30.0	34.5	+4.5	98.2	98.8	+0.6	25.5
2	36, M	Pads over and under abdomen	27.0	35.0	+8.0	26.5	35.5	+9.0	29.0	35.0	+6.0	27.5	35.5	+8.0	97.8	98.6	+0.8	25.0
3	38, M	Pads over and under abdomen	25.5	33.0	+7.5	27.0	33.0	+6.0	29.5	35.0	+5.5	28.5	32.0	+3.5	97.4	98.4	+1.0	25.5
4	26, M	Pads under back; cuff around right thigh	23.0	33.0	+10.0	22.5	33.0	+10.5	26.0	33.0	+6.5	27.0	33.5	+6.5	98.2	99.0	+0.8	25.5
5	38, M	Pads under back; cuff around right thigh	27.5	29.5	+2.0	27.5	28.0	+0.5	29.0	29.5	+0.5	30.0	29.5	−0.5	97.4	97.6	+0.2	25.0
6	28, M	Cable under mattress	25.5	33.5	+8.0	30.0	34.0	+4.0	27.0	33.0	+6.0	30.5	33.5	+3.0	98.0	98.4	0.4	25.5
7	38, M	Cable under mattress	27.0	30.5	+3.5	27.5	30.5	+3.0	28.0	30.0	+2.0	28.0	30.0	+2.0	98.0	98.4	+0.4	25.5
8	36, M	Cable under mattress	25.0	33.5	+8.5	24.5	34.0	+9.5	27.0	32.0	+5.0	26.5	31.5	+5.0	97.4	98.6	+1.2	25.5
9	32, M	Cable under mattress	27.5	34.0	+6.5	27.5	35.5	+8.0	28.5	35.5	+7.0	29.0	35.5	+6.5	98.2	99.4	+1.2	25.5
10	36, M	Cable under mattress	30.0	34.0	+4.0	29.5	33.5	+4.0	30.5	33.5	+3.0	30.5	33.5	+3.0	97.8	98.4	+0.8	25.5
11	30, M	Cable under mattress	25.0	34.0	+9.0	25.0	34.0	+9.0	29.5	33.0	+3.5	29.5	32.5	+3.0	98.8	98.8	0.0	25.5
12	36, M	Cable under mattress	26.0	33.5	+7.5	26.0	34.0	+8.0	27.5	33.5	+6.0	27.0	33.5	+6.5	98.0	98.2	+0.2	25.5
13	28, M	Cable under mattress	29.0	34.0	+5.0	30.0	34.5	+4.5	29.0	33.5	+4.5	29.5	33.0	+4.5	98.0	98.4	+0.4	25.5
14	27, M	Cable under mattress	26.0	34.0	+8.0	26.0	34.5	+8.5	27.5	33.5	+6.0	27.5	33.5	+6.0	98.2	98.6	+0.4	25.5
15	34, M	Cable under mattress	25.0	34.5	+9.5	24.5	34.5	+10.0	28.0	32.0	+4.0	27.5	33.0	+5.5	98.4	98.4	0.0	25.5
16	34, M	Cable under mattress	24.5	35.0	+10.5	24.5	35.0	+10.5	28.0	33.8	+5.8	28.0	33.5	+5.5	98.6	99.0	+0.4	25.5
17	34, M	Cable under mattress	28.0	34.5	+6.5	28.5	34.5	+6.0	27.5	33.5	+6.0	27.5	34.0	+6.5	98.2	99.0	+0.8	25.0
18	28, M	Cable under mattress	26.0	34.5	+8.5	25.5	35.0	+9.5	30.0	34.0	+4.0	29.0	34.0	+5.0	98.0	99.0	+1.0	28.0
19	27, M	Cable under mattress	25.5	34.0	+8.5	24.5	34.0	+9.5	28.0	33.0	+5.0	30.5	33.5	+3.0	98.6	99.0	+0.4	25.0
20	29, M	Cable under mattress	29.0	34.5	+5.5	28.0	34.5	+6.5	30.0	35.0	+5.0	29.5	35.0	+5.5	98.2	98.4	+0.2	25.5

with the temperature of the dorsum of the feet lagging behind 1.0 to 1.5° C. The curve ascends sharply during the first ten minutes, indicating a prompt peripheral vasodilating response. This result is in marked contrast to the first ten-minute change seen in determinations made on patients who have organic arterial occlusive disease, in observations of whom no change may be discovered. The rate of increase, however, cannot be considered as characteristic, since it will be modified greatly with different resting temperatures. Thus, in a normal patient with a resting skin temperature of the toes of 30.0° C., the temperature may increase only 0.5° C. in the first ten minutes of irradiation.

The seven studies made of five patients who had essential hypertension (grades 2 to 3) were similar in results to those of normal subjects (Table II). The rate and intensity of the increase in temperature of the skin seemed in no way to be characteristic.

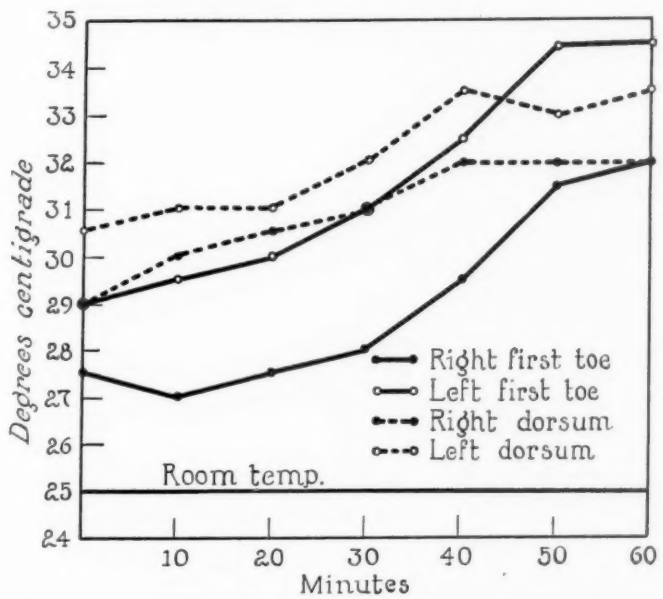

Fig. 2.—Changes in temperature occurring in observation 9 (Table III), after sixty minutes of application of heat. The patient was suffering from arteriosclerosis obliterans.

Eighteen observations were made on thirteen patients who had arteriosclerosis obliterans (Table III). The temperature of the skin of both first toes of twelve of these patients increased. The temperature of the left first toe of one patient remained unchanged. The mode rise was to a maximum of 31.5° C. The average increase in oral temperature was 0.65° F.

Fig. 2 (observation 9, Table III) reveals a slow change in temperature reaching its maximal height in fifty to sixty minutes. The temperature of the left first toe increased slowly to a normal value, but the tempera-

TABLE II

CHANGES IN TEMPERATURE OF THE SKIN OF THE TOES AND FEET, AND OF THE MOUTH: SEVEN OBSERVATIONS ON FIVE PATIENTS SUFFERING FROM ESSENTIAL HYPERTENSION

OBSERVATION	GRADE OF ESSENTIAL HYPERTENSION	AGE (YR.) AND SEX OF PATIENT	MODE OF APPLICATION OF DIATHERMY	FIRST TOE, PLANTAR SURFACE (°C.)						DORSUM OF FOOT (°C.)						ORAL TEMPERATURE (°F.)			ROOM TEMPERATURE (°C.)
				RIGHT			LEFT			RIGHT			LEFT						
				REST	AFTER DIATHERMY	CHANGE	REST	AFTER DIATHERMY	CHANGE	REST	AFTER DIATHERMY	CHANGE	REST	AFTER DIATHERMY	CHANGE	REST	AFTER DIATHERMY	CHANGE	
1	2+	36, F	Cable under mattress	27.5	35.0	+7.5	27.5	35.5	+8.0	31.5	35.0	+4.5	31.5	35.0	+4.5	97.4	99.0	+1.6	25.5
2	3	30, M	Cable under mattress	28.5	33.0	+4.5	27.5	33.0	+4.5	30.5	32.0	+1.5	31.5	32.0	+0.5	98.6	99.0	+0.4	25.0
3	3	35, M	Cable under mattress	25.5	33.0	+7.5	25.5	33.0	+7.5	28.0	32.0	+4.0	27.5	32.0	+4.5	97.4	98.4	+1.0	25.0
4	3	35, M	Cable under mattress	28.5	34.0	+5.5	28.5	34.0	+5.5	30.0	32.5	+2.5	30.0	32.5	+2.5	97.8	99.0	+1.2	25.0
5	2+	40, M	Cable under mattress	26.0	33.5	+7.5	25.5	34.5	+9.0	28.5	32.0	+3.5	30.5	33.5	+3.0	99.0	99.4	+0.4	25.0
6	2	39, M	Cable under mattress	26.0	34.5	+8.5	26.5	34.5	+8.0	29.0	33.5	+4.5	29.0	33.0	+4.0	98.0	98.8	+0.8	25.5
7	2+	36, F	Cable around left thigh	30.5	33.5	+3.0	30.5	34.0	+3.5	31.0	34.0	+3.0	31.0	34.5	+3.5	97.6	98.4	+0.8	25.5

TABLE III

CHANGES IN TEMPERATURE OF THE SKIN OF THE TOES AND FEET, AND OF THE MOUTH: EIGHTEEN OBSERVATIONS ON THIRTEEN PATIENTS SUFFERING FROM ARTERIOSCLEROSIS OBLITERANS

OBSERVATION	AGE (YR.) AND SEX OF PATIENT	MODE OF APPLICATION OF DIATHERMY	FIRST TOE, PLANTAR SURFACE (°C.)						DORSUM OF FOOT (°C.)						ORAL TEMPERATURE (°F.)			ROOM TEMPERATURE, (°C.)
			RIGHT			LEFT			RIGHT			LEFT						
			REST	AFTER DIATHERMY	CHANGE	REST	AFTER DIATHERMY	CHANGE	REST	AFTER DIATHERMY	CHANGE	REST	AFTER DIATHERMY	CHANGE	REST	AFTER DIATHERMY	CHANGE	
1	64, M	Cable under mattress	30.0	32.0	+2.0	30.0	30.0	0.0	30.0	32.5	+2.5	31.5	32.0	+0.5	98.6	98.8	+0.2	26.0
2	58, M	Cable under mattress	25.0	30.0	+4.0	25.0	29.5	+4.5	27.0	29.5	+2.5	27.5	29.5	+2.0	98.4	99.0	+0.6	25.5
3	51, M	Cable under mattress	Amputated			31.0	32.0	+1.0	Amputated			32.5	33.5	+1.0	98.4	98.6	+0.2	25.5
4	51, M	Cable under mattress	Amputated			29.0	31.0	+2.0	Amputated			30.5	32.5	+2.0	97.8	98.2	+0.4	25.5
5	45, M	Cable under mattress	28.5	32.0	+3.5	31.5	34.0	+2.5	31.5	33.5	+2.0	33.0	35.0	+2.0	98.2	98.6	+0.4	25.0
6	65, M	Cable under mattress	28.5	31.0	+2.5	27.0	29.0	+2.0	30.5	32.0	+1.5	30.0	31.0	+1.0	98.0	99.0	+1.0	25.0
7	65, M	Cable under mattress	27.0	31.5	+4.5	27.5	29.5	+2.0	30.0	31.0	+1.0	29.5	30.5	+1.0	97.4	98.4	+1.0	25.0
8	61, M	Cable under mattress	26.5	30.5	+3.5	28.5	34.5	+6.0	29.5	32.5	+3.0	30.5	34.0	+3.5	98.6	99.0	+0.4	25.0
9	61, M	Cable under mattress	27.5	32.0	+4.5	29.0	34.5	+5.5	29.0	32.0	+3.0	30.5	33.5	+3.0	98.4	98.8	+0.4	25.0
10	62, F	Cable under mattress	29.0	32.0	+3.0	29.5	32.0	+2.5	30.0	30.5	+0.5	29.5	31.5	+2.0	98.6	98.8	+0.2	25.0
11	66, M	Pad under back; Cuff on right thigh	28.0	31.0	+3.0	29.0	32.5	+3.5	31.0	31.0	0.0	31.0	32.0	+2.0		98.8		25.0
12	51, M	Pads over and under abdomen	Amputated			29.5	31.5	+2.0	Amputated			30.0	33.5	+3.5	98.2	98.8	+0.6	25.5
13	40, M	Cable around right thigh	25.0	27.0	+2.0	27.5	31.5	+4.0	28.0	31.5	+3.5	29.0	33.0	+4.0	98.2	98.8	+0.6	25.5
14	60, M	Cable around right thigh	30.5	33.5	+3.0	27.0	29.5	+2.5	29.0	31.0	+2.0	30.5	34.0	+3.5	98.2	98.8	+0.6	25.5
15	52, M	Cable around right thigh	29.5	32.0	+2.5	29.0	32.5	+3.5	30.0	33.0	+3.0	29.5	33.5	+4.0	97.8	99.0	+1.0	25.5
16	60, M	Cable around left thigh	28.5	33.0	+4.5	27.0	30.0	+3.0	29.0	30.5	+1.5	29.5	34.5	+5.0	98.0	98.8	+0.8	25.5
17	52, M	Cable around left thigh	25.0	30.5	+5.5	23.0	28.5	+5.5	29.0	31.5	+2.5	24.5	28.5	+4.0	97.4	98.4	+1.0	25.0
18	48, M	Cable around left thigh	29.0	31.5	+1.5	30.5	32.5	+2.0	30.0	32.5	+2.5	31.5	33.0	+1.5	97.4	99.2	+1.8	25.0

ture of the right toe lagged to the extent of 2.5° C. at the end of sixty minutes. The indications of this curve correspond to the clinical findings in this case. The patient was admitted to the Mayo Clinic two weeks prior to the making of the observations, suffering from acute occlusion of the right popliteal artery. The foot had responded well, but slowly, to routine conservative measures.

Thirteen observations were performed on nine patients who had thrombo-angiitis obliterans (Table IV). The temperatures of the skin of the first toes were increased over the resting values in all cases. In several instances the skin temperature rose to 31.5° C., with a secondary rise to 34.0° C. The increase in oral temperature averaged 0.7° F.

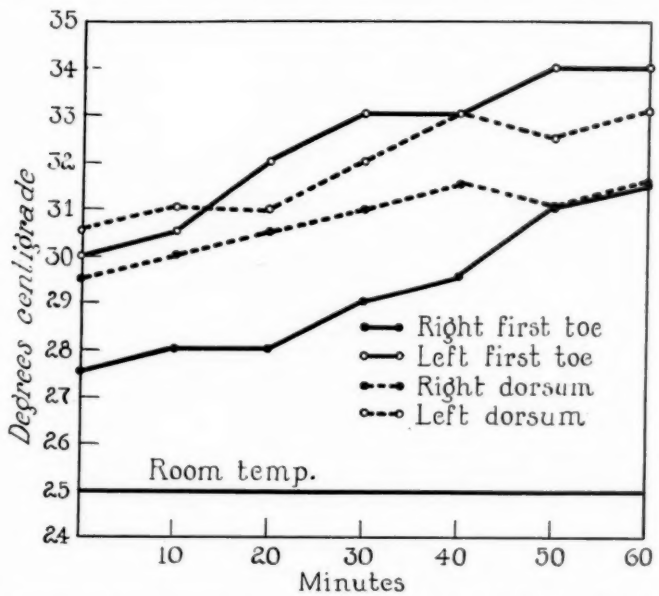

Fig. 3.—Changes in temperature occurring in observation 8 (Table IV) after sixty minutes of application of heat on a patient suffering from thromboangiitis obliterans.

Fig. 3 (observation 8, Table IV) indicates the changes in temperature of the skin in a typical observation in this series. The left foot reacted in such a manner that the curve could not be distinguished from a curve in our normal series. The temperature of the right first toe increased very slowly, whereas the dorsum of that foot reacted in a more nearly normal manner.

An attempt was made to learn whether short-wave diathermy would bring about a higher temperature of the feet than could be produced by the several other methods mentioned in both the literature and in the first part of this paper. Ten such studies were carried out; in eight of these diathermy succeeded, and in two it preceded the other methods of warming. In six of the ten instances one upper extremity of the subject was immersed to the midportion in a large tub of water which was

TABLE IV

CHANGES IN TEMPERATURE OF THE SKIN OF THE TOES AND FEET, AND OF THE MOUTH: THIRTEEN OBSERVATIONS ON NINE PATIENTS SUFFERING FROM THROMBOANGIITIS OBLITERANS

OBSERVATION	AGE (YR.) AND SEX OF PATIENT	MODE OF APPLICATION OF DIATHERMY	FIRST TOE, PLANTAR SURFACE (°C.)						DORSUM OF FOOT (°C.)						ORAL TEMPERATURE (°F.)			ROOM TEMPERATURE, (°C.)
			RIGHT			LEFT			RIGHT			LEFT						
			REST	AFTER DIATHERMY	CHANGE	REST	AFTER DIATHERMY	CHANGE	REST	AFTER DIATHERMY	CHANGE	REST	AFTER DIATHERMY	CHANGE	REST	AFTER DIATHERMY	CHANGE	
1	45, M	Cable under mattress	28.5	31.5	+3.0	29.5	31.5	+2.0	30.0	31.5	+1.5	30.5	31.5	+1.0	98.6	99.2	0.6	25.5
2	31, M	Cable under mattress	31.0	34.0	+3.0	31.5	34.0	+3.5	31.0	32.5	+1.5	31.5	33.0	+1.5	97.6	98.2	+0.6	25.5
3	54, M	Cable under mattress	33.0	35.0	+2.0	30.0	31.5	+1.5	33.5	35.0	+1.5	31.5	33.0	+1.5	97.8	98.6	+0.8	25.5
4	32, M	Cable under mattress	31.0	34.5	+3.5	30.5	32.0	+1.5	31.5	33.5	+2.0	31.0	31.0	0.0	97.2	98.2	+1.0	25.5
5	36, M	Cable under mattress	26.5	29.5	+3.0	27.5	31.0	+3.5	28.5	29.0	+0.5	29.5	31.0	+1.5	98.2	98.6	+0.4	25.5
6	40, M	Cable under mattress	29.0	31.5	+1.5	Amputated			30.5	32.5	+2.0	Amputated			98.8	99.2	+0.4	25.5
7	52, M	Cable under mattress	Amputated			29.0	33.0	+4.0	Amputated			29.5	34.0	+4.5	97.6	98.6	+1.0	30.0
8	50, M	Cable under mattress	27.5	31.5	+4.0	30.0	34.0	+4.0	29.5	31.5	+2.0	30.5	33.0	+2.5	98.0	98.4	+0.5	25.0
9	32, M	Cable under mattress	28.5	31.5	+3.0	26.0	30.0	+4.0	28.5	31.0	+2.5	28.0	32.0	+4.0	97.8	98.8	+1.0	25.0
10	32, M	Cable under mattress	27.0	32.0	+5.0	26.0	30.5	+4.5	29.0	31.0	+2.0	29.0	32.0	+3.0	98.0	98.4	+0.4	25.0
11	32, M	Pads over and under abdomen	32.0	34.0	+2.0	31.0	31.5	+0.5	32.0	32.0	0.0	31.5	31.5	0.0	98.2	98.8	+0.6	25.5
12	36, M	Pads over and under abdomen	27.5	29.0	+1.5	28.5	30.5	+2.0	30.0	30.0	0.0	30.5	31.0	+0.5	98.0	98.8	+0.8	25.5
13	45, M	Pad under back; Cuff on right thigh	27.5	32.5	+5.0	29.5	32.5	+3.0	29.5	32.0	+2.5	30.0	32.5	+2.5	98.4	99.2	+0.8	25.5

maintained at a temperature of between 112 and 115° F. (44.4 and 46.1° C.). An infrared luminous baker was applied to one upper extremity of each of two other subjects, and the luminous infrared source was applied to the lower portion of the abdomen of each of the remaining two. As has been said, in eight of these ten instances short-wave diathermy was applied immediately following one hour of this comparison heating. In each of these cases, following application of diathermy, there was an additional rise in skin temperature ranging from

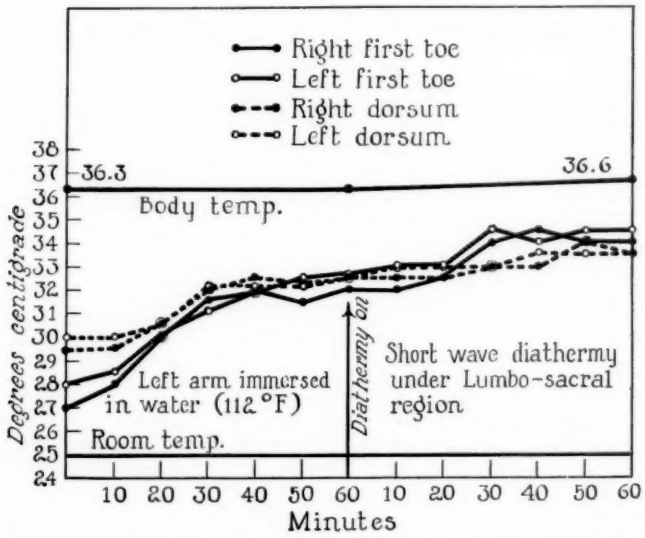

Fig. 4.—Comparative changes in temperature obtained by immersion of left arm of a subject for sixty minutes in water of 112° F. (44.4° C.) temperature, and by subsequent application of short-wave diathermy for sixty minutes under the lumbosacral region.

0.5 to 7.0° C. The average additional rise was 3.1° C. In the remaining two of the ten instances, as was said above, the comparison warming was effected immediately following one hour of application of diathermy. This resulted in a fall in skin temperature during the warming period, which averaged 2.5° C. Fig. 4 represents a typical observation in this series. We realize that the arrangement employed cannot be considered to have furnished a scientific comparison because we have no way of determining the intensity of heat induced by diathermy. Further, in all cases the systemic (oral) temperature was elevated by short-wave diathermy, whereas control methods brought about no appreciable change.

COMMENT

When the observations reported in this paper were started, we had some hope that the changes in rate and intensity of the temperature of the skin during application of short-wave diathermy might prove to be of prognostic, or even of diagnostic, value. We thought it might be

possible that a graph of a standard, closely controlled study might be "read" as a guide to diagnosis and prognosis. However, it soon became evident that too many variables existed to expect consistent response even from the clinically normal patient. We realized from the first that we would be unable to apply high frequency current to each patient with identical intensity, because of the present inability to measure the amount of heat actually given to the patient. An identical cable electrode apparatus would minimize this particular variable, but differences in thickness and consistency of subcutaneous tissue introduce further variable factors. However, such variability is minor, when compared with the inherent difference in vascular response seen in studies of clinically normal subjects. Observations 5 and 7, Table I, illustrate this point well. In these observations on the same subject, the temperature of the skin failed to increase appreciably during the hour of irradiation. The subject was a tall, thin person whose chief reason for coming to the clinic was coldness of the feet. Years before, he had sustained a compound fracture of the lower third of the left tibia and fibula, which had healed with some deformity and narrowing of the leg in that region. The arterial supply and venous return appeared to be normal and no clinical vascular differences existed between the two limbs. No explanation for this man's failure to respond to the diathermy heating can be offered. Several investigators[5, 16-18] have reported instances in which peripheral vasodilation in the lower extremities of normal persons failed to occur following warming of an upper extremity. In retrospect, we believe that had this subject's bodily temperature been elevated a degree or so higher, the peripheral capillaries might suddenly have been released of their constriction.

To obtain comparable records it also would be necessary that each subject's skin temperature be at the same value when application of short-wave diathermy is begun. We made no attempt to do this, partly because we did not wish to cool unduly the extremities of patients who had organic vascular disease, and also because the ultimate height of temperature is far more important than the number of degrees of change in temperature.

It is of therapeutic value to know how long the increase in oral and skin temperature may persist following cessation of application of diathermy. In each observation of this series, the oral and skin temperatures were determined at fifteen-minute intervals for one hour after the current had been turned off. The results were as might be expected of partially nude subjects in an environmental temperature of 25.0 to 25.5° C. The oral temperature dropped to within normal limits in fifteen to thirty minutes. The skin temperatures decreased in similar fashion, but the feet of the normal subject usually were warmer at the end of the hour following cessation of application of short-wave diathermy than before the diathermy had been applied. In the presence of deficient arterial circulation, the decrease in temperature was of a

rapidity comparable to that of decrease of the temperature of normal subjects. However, because the maximal rise usually had been less than that observed in studies of normal subjects, the skin temperatures at the end of the hour closely approximated the previous temperatures at rest. These studies show that in our work the increased oral and skin temperatures are not maintained usually for longer than thirty minutes after cessation of application of diathermy. However, the increased oral and skin temperature induced by the diathermy may be maintained indefinitely by inhibiting the loss of heat through the skin. This may be done by covering the subject, with the exception of his head, with a cotton sheet and woolen blanket. We know from our experience with fever therapy that if a patient is surrounded by an insulating material, progessive hyperpyrexia will develop, and that the body temperature will be in direct relationship to the efficiency of the insulation and to the period over which the insulation is applied. It is thus easily possible to maintain the oral temperature of a patient at 99 to 100° F. for several hours or longer.

Application of short-wave diathermy in the clinical management of peripheral arterial occlusive disease seems indicated because of the favorable response thereto, as represented by the temperature of the skin. This study, however, was not to determine whether short wave diathermy was superior to other means of promoting vasodilation and, therefore, increased temperatures of the skin. We do feel that short-wave diathermy is an efficient means of inducing heat in the human body and, for this reason, its use should be considered in the care and study of patients with peripheral vascular disease.

It is to be remembered that the use of these high-frequency currents may be dangerous and that they should be applied only by persons trained in their application. If such care is observed, there is little, if any, danger. Because of the danger, however, we cannot advise their use in the home under the patient's control. Since overheating of any metal within the high-frequency field may occur, diathermy should not be applied over an inner-spring mattress. The current is most safely applied when the patient is lying on a wooden pallet covered by a hair mattress.

SUMMARY AND CONCLUSIONS

1. Short-wave diathermy applied to the trunk of the human body is a safe and efficient means of producing peripheral vasodilation of the lower extremities and, as such, should be of value in the management and study of peripheral vascular disease.

2. The use of the electromagnetic cable in a pancake formation under the lumbosacral region was found to be simpler in application and more comfortable in use than were several other possible applications of electrodes, and as efficient in operation as any of the other possible applications.

3. Short wave diathermy should be employed in the treatment of patients with peripheral vascular disease only under careful medical supervision.

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CRYSTAL MICROPHONE FOR PULSE WAVE RECORDING

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TWO years ago a research on the deep systolic jugular pulse in tricuspid valve disease and in chronic "functional" tricuspid regurgitation by White and Cooke[1] occasioned the desire and demand for a simple method of simultaneously recording the electrocardiogram and pulsation in arteries or veins by means of paired galvanometers which would be more convenient than a galvanometer and the Frank capsule. There resulted a very satisfactory adaptation of the crystal microphone for pulse wave recording. Fig. 1 shows one of the simultaneous tracings of electrocardiogram and jugular pulse obtained at that time. It should be added that the connection may, of course, be made between the crystal microphone and a single galvanometer to obtain any solitary pulse tracing desired.

Various mechanical methods have been employed for many years to record the pulse wave. Some make use of lever systems in direct contact with the skin, so that the skin motion is magnified, and the tip of the final lever traces out the record on a moving surface. Other devices couple the lever system to the skin by an air column contained within a piece of rubber tubing. A pickup device (glycerine pelotte or a funnel) is applied to the skin and connected to one end of the tubing. The opposite end of the tubing is connected to a receiving tambour whose diaphragm actuates a recording lever system.

The vibration characteristics of these lever systems unfortunately are not suited to accurate recording of the pulse wave for two reasons. Their deflection speed is usually so slow as to obscure rapid fluctuations in the graph, and they are often not properly damped, so that they have a tendency to produce spurious vibrations in the record as a result of their own oscillation. In addition, slow deflection speed is accompanied by an apparent time lag in the recording of the pulse wave details. For example, the peak of the wave may appear on the tracing as if it occurred some time after the true peak pressure has been reached. When the natural frequency of vibration of the lever system is 5 cycles per second, an average figure for many mechanical recorders, this lag may be as much as 0.04 second. Such an error would be serious if an attempt were made to correlate the pulse wave with other cardiac events.

In an attempt to remove the distortion caused by slow deflection speed, an optical rather than a mechanical recording system was used and brought to a high state of perfection by Frank.[2] The air column

From the Cardiac Laboratory of the Massachusetts General Hospital, Boston, Mass., and the Sanborn Company, Cambridge, Mass.
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coupling is retained, but the diaphragm at the far end of the tube carries a mirror which is arranged to twist as the diaphragm moves under the influence of the air pressure variations within the rubber tubing. A beam of light reflected from this mirror acts as an optical lever which is capable of providing a greatly magnified record of the mirror movement on a photographic film, without in any way adding to the inertia of the moving parts. This optical method can be made to have a deflection speed which is satisfactory for pulse recording. The damping is not easily controlled, but, if the deflection speed is great enough, no serious distortion will be introduced even if the device is not critically damped. The sensitivity of this apparatus is fixed by the particular diaphragm used and the distance from mirror to camera and is, therefore, not easily adjusted to suit varying conditions. The connection of the patient to the recording device by a length of rubber tubing introduces a time lag between the pulse and the motion of the recorder which depends upon the length of the tubing; this error in timing may be significant when the pulse is recorded simultaneously with some other cardiac event.

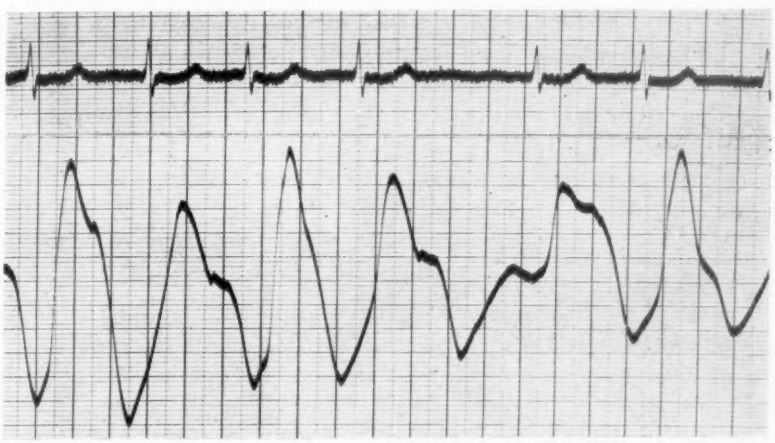

Fig. 1.—Simultaneous electrocardiogram (Lead I, above) and deep jugular pulse on the right side in a case of a woman, aged 49 years, with rheumatic heart disease, mitral stenosis, auricular fibrillation, and probable tricuspid valve disease. Note that frequently, especially during the longer diastolic periods, a stasis wave begins in the neck before systole, followed by the superimposition of the systolic jugular pulse 0.1 to 0.15 second after the upstroke of the R wave. The deep jugular pulse tracing was taken in the upright position with the receiver held over the sternocleidomastoid muscle and connected to a microphone, which was, in turn, attached to the string of one of the paired galvanometers. Time 0.1 second and 0.2 second. (This figure was published in the Transactions of the Association of American Physicians for 1939.)

The recording of the electrocardiogram is, of course, an electrical process. Heart sounds, although they have been recorded by the Frank method, are now almost universally recorded electrically. It would seem, therefore, that an electrical method of recording the pulse is desirable because of the greater ease of controlling the deflection speed, damping, and sensitivity, because of the possibility of eliminating long air columns, and finally, because of the simplification of technique which would result,

especially when the pulse tracing is recorded simultaneously with the electrocardiogram, the phonocardiogram, or both. The electrical method requires, first, changing the skin motion into electrical energy by some form of microphone. This may involve a short air column coupling from the skin to the diaphragm of the microphone. The output of the microphone, which will consist of a series of electrical impulses occurring at the cardiac rate, can then be recorded by a standard electrocardiograph amplifier and galvanometer system. The translation of the mechanical force (the pressure in the rubber tubing leading from the pickup device) into an electrical quantity may be accomplished by two fundamentally different methods. The first of these allows the mechanical force to control some variable element of an electrical circuit so that the current flowing in that circuit will vary in accordance with the applied force.

An example of this method is the ordinary carbon-grain telephone transmitter, which forms a variable resistance element in its associated circuit; this resistance is controlled by the force applied to the transmitter diaphragm. A sphygmograph using a carbon grain microphone and lever actuated by a solenoid was described by Waud[3] in 1924, and in 1928, Turner[4] introduced a sphygmograph made up of a carbon grain microphone and string galvanometer. The carbon microphone has not been satisfactory for measurement or recording work because of its instability and its generation of internal noise. Other possibilities in this control method are the uses of condenser[5] or inductance elements as the microphone. Although these devices are stable and noiseless, the relative complexity of the circuits with which they must be associated has hindered their general adoption for clinical applications.

The second method of changing mechanical into electrical quantities is the generation method, whereby the mechanical energy actuates some form of electrical generator which converts the mechanical energy directly into electrical energy. One form of generator which appears to be peculiarly adapted to the particular problem of pulse recording is the crystal microphone. This device is based upon the property which some crystals have of generating an electrical voltage when the crystal itself is twisted or squeezed; the magnitude of the voltage is proportional to the applied force. The electrical energy is led off from the crystal by thin, metal-foil electrodes, cemented to opposite faces of the crystal. The combination of the electrodes and crystal, when no pressure is applied to the crystal, forms a condenser of definite capacity. When pressure is applied to the crystal, the condenser appears to have had a generator added to it. Electrically, therefore, the crystal microphone may be represented by a generator in series with a condenser, as shown in Fig. 2. The electrical energy developed within the crystal is too small to be used directly with recording instruments. It is necessary, therefore, to insert an amplifier between the microphone and

recording instrument. The load which the amplifier presents to the microphone will be essentially a resistance (the grid leak of the first tube). The voltage delivered to the amplifier (Ea) will differ from that developed by the microphone (E*i*) because of the presence of the condenser (C). The distortion introduced by the capacity C is a function of the rate at which the voltage E*i* is varying and the relative sizes of C and R (resistance). The relative sizes of C and R can be gauged by a single factor, namely, their product RC, known as the "time constant"

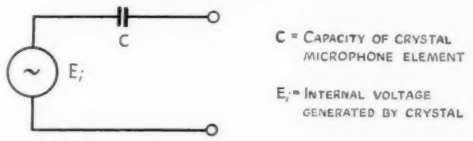

FIG. 2

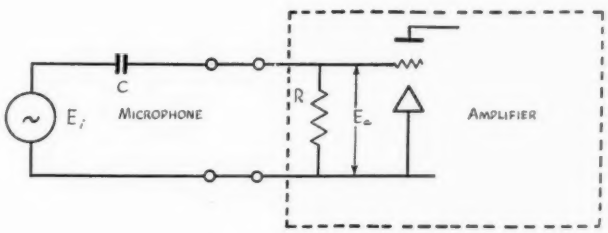

FIG. 3

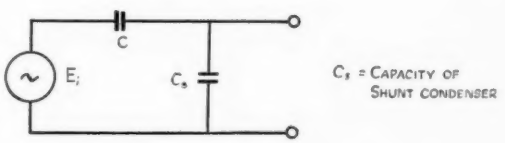

FIG. 4

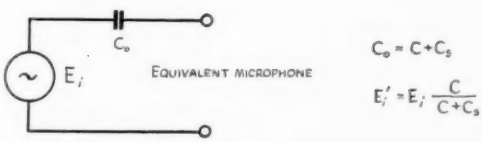

FIG. 5

Figs. 2-5.

of the RC circuit. If C is measured in microfarads and R is given in megohms (1 megohm equals 1,000,000 ohms), this product gives the time constant directly in seconds.

In order that the voltage delivered to the amplifier shall be a reasonably accurate copy of the voltage generated by the microphone, and,

if we bear in mind that the generated voltage is varying at the rate of the heartbeat, it is necessary that the time constant be of the order of several seconds. This question of the relation of the time constant of recording circuits to the rate of variation of the voltage to be recorded has been discussed in a quantitative manner in a paper by Schwarzchild and Kissin.[6]

The capacity of the crystal elements used in microphones is of the order of only several thousandths of a microfarad. The value of R, therefore, would have to be about 1,000 megohms in order to satisfy the requirement that the product RC shall be several seconds. The use of an amplifier input resistance of such an enormously high value is not practical, however, because of the unavoidable shunting effect of leakages through the crystal, the wiring, and the grid current taken by the first amplifier tube. It is this practical limitation which renders the crystal microphone in its usual form unsuitable for pulse wave recording.

In order that the amplifier input resistance be kept at a reasonable value (several megohms), the microphone capacity would have to be of the order of 1 microfarad. The capacity of the crystal microphone may be artificially increased by the simple expedient of shunting an external fixed condenser across it, as shown in Fig. 4. If the circuit of Fig. 4 is analyzed, it will be found to be exactly equivalent to a new microphone whose capacity is represented by CO and whose internal voltage is Ei'. It is seen that the microphone may be given any desired capacity, but that the available voltage is reduced in the same ratio as the capacity is increased. The choice of the shunt capacity becomes a compromise between large capacity and more accurate recording on the one hand, and small capacity and higher output on the other hand.

Fortunately, the pressure variations obtainable from the pulse are so great in comparison with the sound pressure variations for which the microphone is designed, and the inherent crystal microphone sensitivity is so high that, even after reducing the sensitivity and raising the capacity several hundred times by the use of a 1-microfarad shunt condenser, the available output voltage is still in the neighborhood of 1 millivolt. A millivolt impulse is of the correct magnitude to be easily recorded by a standard amplifier type of electrocardiograph. When a standard amplifier type of electrocardiograph is available, and, if its input resistance is several megohms, a crystal microphone may be adapted for pulse wave recording by shunting a 1-microfarad condenser across it and connecting the combination directly to the electrocardiograph input.

When it is desired to use a string galvanometer as the recording instrument, it will be necessary to design a suitable amplifier to couple the crystal to the string, because the low resistance of the string precludes its use directly.

The microphone itself should be mounted in an airtight housing, so that the air column of the pickup device (funnel or pelotte), the rubber tubing, and the microphone diaphragm form a completely sealed space. The skin motion is then converted into pressure variations within this enclosed volume of air which actuate the microphone diaphragm.

Since the wires from the microphone to the recording equipment may be any length and the microphone is small and requires no elaborate supporting fixtures, the rubber tubing between microphone and pickup need be only a few inches in length. This avoids the time lag introduced by the transmission of air pressure variations through long tubes.

The deflection speed and damping of a properly adjusted electrocardiograph are such as to insure accurate recording of the pulse, which is relatively less complicated and contains more slowly varying waves than the electrocardiogram itself. Continuous control of the sensitivity over a wide range, which is not practical with the mechanical systems or with the Frank capsule, is, of course, easily accomplished with the sensitivity control with which the electrocardiograph is already equipped. The possible distortion introduced by the coupling condenser effect of the microphone itself, or by the condensers within the amplifier, does not change the timing of the events in the pulse cycle, and therefore it does not impair the diagnostic value of the resulting curves. It is simply an addition to the possible distortion already unavoidably introduced into the recording system by the interposition of the wall of the blood vessel and its surrounding tissues.

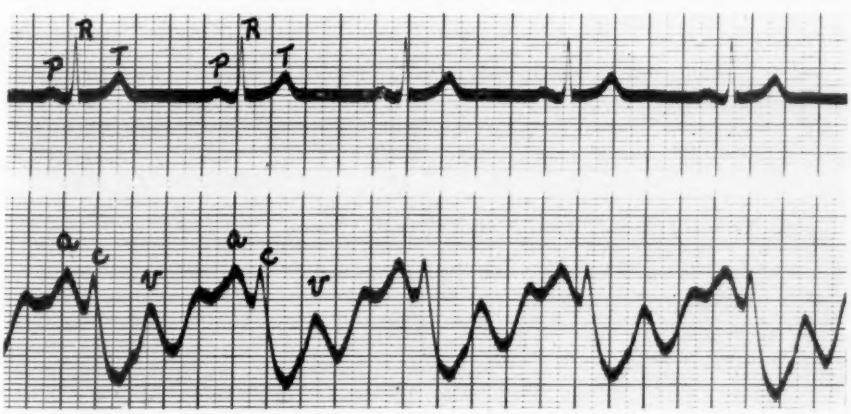

Fig. 6.—Simultaneous Lead II of the electrocardiogram, above, and jugular pulse tracing by the use of the crystal microphone and string galvanometer, below, in the case of a healthy young man.

A photograph of the crystal microphone (piezoelectric) sphygmographic attachment for use with the galvanometer was published by Rappaport and Sprague in their paper entitled "Physiologic and Physical Laws That Govern Auscultation, and Their Clinical Application."*

*AM. HEART J. 21: 257, 1941; see Fig. 21.

Fig. 6 is an example of a normal jugular pulse tracing taken by the use of the crystal microphone simultaneously with Lead II of the electrocardiogram.

SUMMARY AND CONCLUSIONS

Pulse wave recordings obtained indirectly by instruments coupled to the skin may be affected by the blood vessel wall and surrounding tissues, but this effect is not of great clinical significance, whereas the important requirements of correct timing of pulse wave details and freedom from spurious waves cannot be met by purely mechanical recorders and are met with difficulty by optical devices. Neither of these types of recorders is especially convenient, particularly when simultaneous tracings of the pulse and other cardiac events are taken.

These difficulties may be overcome by electrical recording methods. Specifically, we have shown how a crystal microphone may be adapted to give satisfactory pulse tracings by using an electrocardiograph amplifier and galvanometer as the recording system.

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THE CIRCULATORY ADJUSTMENTS IN POLYCYTHEMIA VERA

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FEW observations of the cardiac output and related functions of the circulation have been made on patients suffering from polycythemia vera. The earlier observations of Bergmann and Plesch,[1] Loewy,[2] Mohr,[3] and Röver[4] revealed no significant variation in cardiac output from normal. Liljestrand and Stenström,[5] using the method of Krogh and Lindhardt, found a decrease of 10 per cent in the cardiac index, while Ernst[6] found an increase of 10 per cent. More recently Goldsmith[7] has made observations employing the acetylene method of Grollman. In one patient, observed for eight months, the cardiac output was elevated when the amount of hemoglobin and the count of the red blood cells were higher than normal, and decreased as these fell toward normal. From an analysis of the case history of this patient, together with the observation of the persistently elevated basal metabolic rate, it is not clear that the changes in the circulation represent the effect of polycythemia vera alone. In two other patients observed by Goldsmith, the values were within normal limits, and in the fourth, the cardiac output was slightly increased. Thus, neither Goldsmith's nor other data in the available literature allow a final conclusion as to what changes occur in the circulation of patients suffering from polycythemia vera.

In an attempt to clarify the present state of our information, we have made studies of the cardiac output, oxygen consumption, cardiac size, left ventricular work, and other related functions of the circulation in six patients suffering from polycythemia vera.

METHODS

All observations were made in the morning while the patients were in a basal metabolic state. Measurements of the cardiac output were made by the acetylene method, three samples of gas being taken as first recommended by Grollman,[8] and as further elaborated by Grollman, Friedman, Clark, and Harrison.[9] The Grollman technique can be applied to these patients since the oxygen saturation of the arterial blood in polycythemia vera, when the patient is at rest, is normal, or only slightly less than normal[10, 11] (Cases 1 and 7, Table II); more-

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over, the solubility of acetylene in polycythemic blood is so slightly less than in normal blood that it makes no appreciable difference in the final calculations (Grollman[12]). During rebreathing, the patients were sitting in a steamer chair (angle 135°) with legs extended. They were acquainted with and trained to carry out the procedures beforehand. While the patient was at rest, the cardiac rate was counted at intervals of five minutes. At the end of one hour the acetylene-air-oxygen mixture was rebreathed. Three samples of gas were taken during each rebreathing period for estimation of the arteriovenous oxygen difference. The first sample was taken after rebreathing 10 to 12 times in 20 seconds, the second after 2 to 3 breaths more, and the third after 2 to 3 additional breaths. All three samples were usually obtained before the end of 30 seconds. Samples were taken during expiration. Two periods of rebreathing were carried out on each patient. Shortly afterwards, the oxygen consumption was measured with a Benedict-Roth spirometer. After a short pause, the vital capacity was measured and height and weight were ascertained. In succession, sufficient time being allowed between each procedure for the patient to return to a basal metabolic state, the three standard leads of the electrocardiogram and a chest lead were taken, the arm-to-tongue circulation time recorded, the venous pressure estimated, the blood pressure measured, and a roentgenogram of the heart made at a distance of two meters.

The arm-to-tongue circulation time was estimated by the use of decholin.[13] Five c.c. of a 20 per cent solution were injected rapidly (1 to 2 seconds) through an 18 gauge needle into an antecubital vein while the patient was lying quietly in the supine position. This was repeated one and one-half minutes after the response to the first test had been elicited. The time was recorded from the beginning of the injection until the patient perceived the bitter taste.

The venous pressure was measured by the direct method,[14] using a large antecubital vein, the arm being placed on a level with the right auricle. The system was filled with normal saline and the venous pressure read directly from a scale as millimeters of saline. Normal pressures by this method range from 40 to 100 mm. of saline.[15] In subsequent measurements the vein was entered at the site first punctured, the vein of one arm being reserved for measurement of venous pressure, and of the other arm for estimation of the circulation time.

Roentgenograms of the heart were taken with the patient in the standing position, in full inspiration, at a distance of two meters. Measurements of the cardiac area were carried out by the technique of Levy.[16]

In two patients (Cases 1 and 7), estimations of the oxygen content of the blood were made. Samples of arterial blood were taken under

albolene from a radial or brachial artery, and of venous blood, without stasis, from an antecubital vein, the same vein being used for this purpose each time. The oxygen content of these samples was estimated by the Van Slyke and Neill manometric method.[17] Samples of blood were taken in the morning before breakfast with the patient in a basal metabolic state.

The effect of the polycythemic state on the work of the left ventricle per beat was calculated by making use of the formula[18] $W = QR + \frac{wV^2}{2g}$, in which W equals work done per beat; Q equals volume of blood expelled per beat; R equals mean arterial blood pressure in mm. of Hg $\times$ 13.6; V equals velocity of blood at aorta; w equals weight of blood; and g equals acceleration due to gravity. The last part of the formula, $\frac{(wV^2)}{2g}$, has been omitted (Starr[19]). By substituting values in the formula, the work of the left ventricle per beat has been calculated. Since there is evidence[20] that the work of the right ventricle bears a constant relationship to that of the left, we have concerned ourselves only with the latter.

OBSERVATIONS

Observations were made on 6 patients suffering from polycythemia vera who exhibited a wide range in the amount of hemoglobin and in count of the red blood cells. In one patient (Case 1), it was possible to make observations not only during the polycythemic state, but also later when anemia had occurred as a consequence of therapy, and again when normal levels of the red blood count and hemoglobin were restored. None of the patients exhibited signs or symptoms of congestive heart failure at the time when observations were made. Examination of the heart revealed no abnormalities except in the case of F. M. (Case 1) who exhibited slight enlargement of the heart.

CASE 1.—F. M., History No. 62980, male, aged 34 years, was admitted to hospital on April 30, 1934. He had observed blueness of the hands and feet for three years, and during this period had suffered from drowsiness and frontal headaches. Examination revealed purplish red cyanosis of the skin and mucous membranes, many small, fresh hemorrhages in both optic fundi, enlargement of the spleen, and edema of the ankles. The count of the red blood cells was 9.4 million and the hemoglobin amounted to 158 per cent. The electrocardiogram showed normal sinus rhythm; right axis deviation was present. A roentgenogram of the heart showed enlargement both to the right and to the left. Treatment with acetylphenylhydrazine, x-radiation, and venesection was instituted. Studies of the circulation were made on May 26, 1934, at a time when the amount of hemoglobin and the count of the red blood cells were far above normal (Table I, Fig. 1), on June 16, 1934, when they were far below normal, as a result of intensive treatment, again on July 27, 1934, during recovery from anemia, and finally on October 11, 1934, and January 9, 1935, when they had attained normal values. Observations relating to the blood gases were made on October 13, 1934 (Table II).

TABLE I

MEASUREMENTS OF THE CIRCULATION IN SIX PATIENTS SUFFERING FROM POLYCYTHEMIA VERA

	AGE, YR.	SEX	DATE	HEIGHT, CM.	WEIGHT, KG.	BODY SURFACE AREA, SQ.M.	OXYGEN CONSUMPTION, C.C. PER MIN.	BASAL METABOLIC RATE, PER CENT	ARTERIOVENOUS OXYGEN DIFFERENCE, C.C.	CARDIAC OUTPUT, L./MIN.	CARDIAC OUTPUT, L./SQ.M./MIN.	HEART RATE, PER MIN.	STROKE VOLUME, C.C. PER BEAT	CARDIAC AREA, SQ.CM.	CARDIAC VOLUME, C.C.	ARTERIAL PRESSURE, MM. Hg	LEFT VENTRICULAR WORK, GM. M./BEAT	CIRCULATION TIME, SEC.	VENOUS PRESSURE, MM. SALINE	VITAL CAPACITY, C.C.	RED BLOOD COUNT, MILLIONS	HEMOGLOBIN,* PER CENT	CARDIO-THORACIC RATIO, PER CENT
Case 1, F. M.	34	M	5/26/34	176.8	86.9	2.04	286	+2	75.5	3.79	1.86	98	39	175.8	1126.3	110/ 85	52.0			3300	7.4	128	52.1
			6/16/34	178.0	84.4	2.03	272	-2	57.0	4.77	2.35	92	52			110/ 75	65.8			3850	3.6	60	
			7/27/34	177.5	87.4	2.06	276	-2	65.1	4.24	2.06	78	54	162.7	1001.2	120/ 76	72.0				3.7	94	50.1
			10/11/34	179.0	93.0	2.12	280	-3	62.2	4.50	2.12	80	56	160.2	980.5	142/ 86	86.8	14.8		3750	5.5	110	48.1
			1/ 9/35	176.5	90.6	2.09	282	-2	63.1	4.47	2.14	86	52	163.2	1007.0	130/ 90	77.8	17.7	45	3900	4.8	94	50.7
Case 2, H. A.	50	F	1/ 8/38	157.5	71.5	1.72	288	+43	96.5	3.00	1.74	92	33	142.2	819.4	165/100	59.7	14.1	54	2050	8.3	160	50.1
Case 3, A. G.	46	M	10/24/34	175.0	77.5	1.93	228	-9	63.4	3.60	1.86	76	47	149.2	880.9	150/ 90	76.7	21.5		4800	7.1	108	45.9
Case 4, L. L.	47	M	1/13/36	162.5	54.3	1.58	209	+2	67.5	3.09	1.96	72	43	122.4	655.1	110/ 80	55.6	17.7	58	3300	6.8	150	44.3
Case 5, I. S.	43	M	11/13/34	162.8	58.2	1.61	220	+4	61.9	3.55	2.20	63	56	137.8	781.8	160/ 90	95.2	12.2		3650	4.7	94	46.8
Case 6, E. D.	47	F	1/ 8/40	161.0	68.3	1.72	224	+8	77.9	2.87	1.67	74	39	105.2	522.1	124/ 80	54.1	15.8	69	2400	7.5	138	50.9

*14.5 grams equivalent to 100 per cent.

TABLE II

BLOOD GASES IN CASES 1 AND 7

DATE	ARTERIAL BLOOD			VENOUS BLOOD			O_2 CAPACITY ARTERIAL BLOOD VOL. PER CENT	HEMOGLOBIN PER CENT	RED BLOOD CELL VOLUME		RED BLOOD CELL COUNT		OXYGEN UTILIZATION* PER CENT	ARTERIOVENOUS OXYGEN DIFFERENCE† VOL. PER CENT
	O_2 CONTENT VOL. PER CENT	CO_2 CONTENT VOL. PER CENT	O_2 SATURATION PER CENT	O_2 CONTENT VOL. PER CENT	CO_2 CONTENT VOL. PER CENT	O_2 SATURATION PER CENT			ARTERIAL BLOOD PER CENT	VENOUS BLOOD PER CENT	ARTERIAL BLOOD MILLION	VENOUS BLOOD MILLION		
Case 1														
Oct. 13, 1934	19.35	52.92	90.8	12.47	58.85	58.5	21.30	115	50	54	5.80	5.05	32	6.88
Case 7														
Mar. 5, 1926	27.62		95.0	14.74		51.0	29.07	157			8.3		44	12.88
June 24, 1926	29.01		95.5	20.54		68.0	30.17	163			8.2		28	8.47
July 6, 1926	28.72		100.0	18.52		64.4	28.72	155			8.1		35	10.20

*Percentage of oxygen utilization is the ratio between arteriovenous oxygen difference and oxygen capacity.

†From venous arm blood and not mixed venous blood. The arteriovenous oxygen difference from mixed venous blood in Case 1 on 10/11/34 was 62.2 which was very close to that derived from arm blood in this particular instance. This agreement is unusual.

CASE 2.—H. A., History No. 191222, white female, aged 50 years, was admitted to hospital on January 6, 1938. She had suffered from dizziness and flashes of light before the eyes for five years. During this time her complexion had become progressively more florid. Examination showed deep reddish cyanosis of the skin and mucous membranes, distention of the veins of the retinae, generalized venous engorgement, enlargement of the liver to three fingerbreadths below the right costal margin, and of the spleen to two fingerbreadths below the left costal margin. In the electrocardiogram normal sinus rhythm and left axis deviation were present. A roentgenogram of the heart revealed no deviation from the normal. Studies of the circulation were made on January 8, 1938, at a time when the hemoglobin amounted to 160 per cent and the count of the red blood cells was 8.3 million (Table I, Fig. 1).

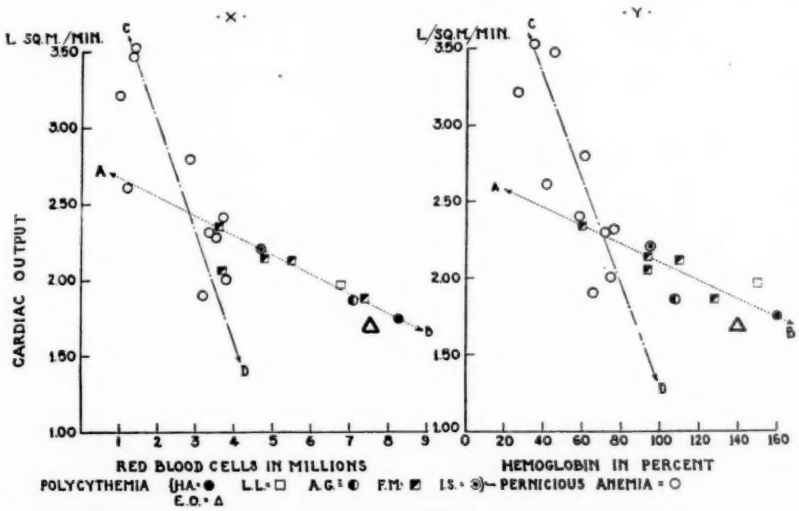

Fig. 1.—Cardiac index, red blood cells and hemoglobin. Counts of red blood cells of patients suffering from polycythemia vera and pernicious anemia are plotted against the corresponding cardiac indices in Fig. 1*X*, while estimations of hemoglobin of the same patients are plotted against corresponding cardiac indices in Fig. 1*Y*. In each instance, there is a linear correlation, in that as the red blood cell count and the amount of hemoglobin increase, the cardiac output decreases. Furthermore, in each instance, the slant of the line for polycythemia vera (line *AB*) is different from that for pernicious anemia (line *CD*). Each symbol represents a patient; a different symbol is used for each patient suffering from polycythemia vera, but the same symbol (open circle) is used for all the patients suffering from pernicious anemia (*21*).

CASE 3.—A. G., History No. 20387, male, aged 46 years, was seen in the Out Patient Clinic on October 24, 1934. He had suffered from intermittent claudication for three years. Examination revealed cyanosis of the lips and the nail beds, florid skin, enlargement of the liver to one fingerbreadth below the right costal margin, and of the spleen to four fingerbreadths below the left costal margin. Electrocardiogram showed right intraventricular heart block and normal sinus rhythm. A roentgenogram of the heart showed no deviation from the normal. Studies of the circulation were made on October 14, 1934, at a time when the hemoglobin amounted to 108 per cent and the count of the red blood cells 7.1 million (Table I, Fig. 1).

CASE 4.—L. L., History No. 48688, male, aged 47 years, was admitted to hospital on December 22, 1936. He had suffered from symptoms of diabetes mellitus for 3 years. Examination revealed dusky cyanosis of the lips, nail beds, and skin, distention of the veins of the retinae, and enlargement of the spleen to two finger-

breadths below the left costal margin. The electrocardiogram was essentially normal. A roentgenogram of the heart showed no deviation from the normal. Studies of the circulation were made on January 13, 1937, at a time when the hemoglobin amounted to 150 per cent and the count of the red blood cells was 6.8 million (Table I, Fig. 1). At the time these studies were made, the diabetes mellitus was controlled by dietetic management and the use of insulin.

CASE 5.—I. S., History No. 55412, male, aged 43 years, was admitted to the Out Patient Clinic in August, 1934. He had suffered from intermittent claudication, dyspnea, substernal oppression on exertion, and attacks of throbbing headache for one year. Examination revealed reddish cyanosis of the mucous membranes, and enlargement of the spleen to the left costal margin. The hemoglobin amounted to 144 per cent and the count of the red blood cells was 6.8 million. Treatment with acetylphenylhydrazine was instituted. On November 13, 1934, the hemoglobin had fallen to 94 per cent and the count of the red blood cells to 4.7 million. On this date, slight cyanosis was still present; the spleen could no longer be palpated. An electrocardiogram showed normal sinus rhythm, and slight changes in the form of the T waves and R-T segments which were thought to be suggestive of coronary artery disease. A roentgenogram of the heart showed no deviation from the normal. Special studies of the circulation were made on November 13, 1934 (Table I, Fig. 1).

CASE 6.—E. D., History No. 28897, white female, aged 47 years, was admitted to hospital on January 2, 1940. She had suffered from headaches, sensation of fullness in the head, and fleeting pain, numbness and tingling in the extremities, for seven years. Examination revealed a plethoric individual, with bluish cyanosis of the lips and nail beds, enlargement of the liver to just below the right costal margin and of the spleen to 7 cm. below the left costal margin. Normal sinus rhythm and left axis deviation were present in the electrocardiogram. In the roentgenogram of the heart, there was no deviation from normal. Special studies of the circulation were made on January 8, 1940, at a time when the hemoglobin amounted to 138 per cent, the count of the red blood cells was 7.5 million and the red blood cell volume was 58 per cent.

In summary, it appears from the data of Table I (Fig. 1) that, when the quantity of hemoglobin and the count of the red blood cells were increased above normal, the arteriovenous oxygen difference was increased and the cardiac output per beat and the cardiac index were decreased. Measurements of the oxygen consumption, heart rate, blood pressure, venous pressure, and the vital capacity showed no consistent variation from the normal. The data concerning the circulation time were insufficient for analysis.

DISCUSSION

These data demonstrate that the increase in red blood cells and in hemoglobin in polycythemia vera is associated with a decrease in volume output of the heart. Furthermore, it appears that increase in the arteriovenous oxygen difference and decrease in the cardiac output is proportional to increase in the amount of hemoglobin and augmented number of the red blood cells, and that these relationships are linear (Fig. 1). For, with the decrease in hemoglobin and in

the count of the red blood cells under therapy, the arteriovenous oxygen difference decreased to normal and the cardiac output increased. When anemia occurred (Case 1), the arteriovenous oxygen difference decreased further still and the cardiac output increased beyond normal, just as we have observed in patients suffering from pernicious anemia[21] (Fig. 1). There appears to be a difference between pernicious anemia and polycythemia vera, however, with respect to the relationships existing between the values for hemoglobin and red blood cells on the one hand, and arteriovenous oxygen difference and cardiac output on the other. When the data from Stewart, Crane, and Deitrick's paper relating to patients suffering from pernicious anemia[21] are plotted on the same chart with those of our six patients suffering from polycythemia vera (Fig. 1), the lines are not continuous as we ascend the scale of values for hemoglobin and red blood cells. The slant of the line for pernicious anemia (Fig. 1, line *CD*) is steeper than that for polycythemia vera (Fig. 1, line *AB*). The increased basal metabolic rate[21] in pernicious anemia no doubt accounts for part of the divergence in the slope of these lines.

In five of these patients (Cases 2, 3, 4, 5, and 6), calculation of the cardiothoracic ratios did not reveal significant change in the size of the heart. In the other patient (Case 1), the cardiothoracic ratio was slightly increased. With respect to the size of the heart, it is of interest to analyze the heart size in relationship to the work of the heart. When the cardiac volumes were plotted as abscissae and the grammeters of work of the left ventricle as ordinates, in accordance with the method of Starr and his co-workers,[19, 22] we noted that all our observations except one fell within the zone of normal circulatory function, indicating that the work of the heart was commensurate with its size.

Since none of our patients exhibited symptoms or signs of heart failure, and since rise in venous pressure was not recorded either in our patients or in those reported by Gibson, Harris, and Swigert,[23] and since the work of the heart in our patients was commensurate to its size, it appears to us that the increase in the arteriovenous oxygen difference and the decrease in cardiac output per beat and cardiac index which we have observed results not directly from impairment of cardiac function in polycythemia vera, but rather as a consequence of, and in order to compensate for, the abnormalities resulting from increase in the amount of hemoglobin and the count of the red blood cells.

In polycythemia vera the blood volume,[23, 24] and viscosity[24, 25] are increased, the velocity of blood flow is decreased,[23] and the capillaries throughout the body exhibit engorgement and retardation of the

blood flow through them,[26, 27] and from these data now being presented, the minute volume output of blood is decreased. The slowing and stagnation of the circulating blood results in lowering of the oxygen content of the venous blood, and provides an explanation of the increased arteriovenous oxygen difference which we observed in our patients, in whom neither symptoms nor signs of heart failure nor increases in the basal metabolic rate were observed. This notion is further borne out by the increase in percentage oxygen utilization observed in one of our patients (Case 6, Table II). Furthermore, in polycythemia vera there is marked increase in the oxygen content of the arterial blood[10, 11] (Case 7,* Table II). Since each unit volume of polycythemic blood contains an unusually large quantity of hemoglobin, the oxygen requirement of the tissues can be satisfied by a cardiac output which is smaller than normal, and the maintenance of a normal cardiac output under these circumstances would impose needless work on the heart. It appears likely, therefore, that the decrease in cardiac output which we observed in our patients represents adaptation of the circulatory mechanism to avoid needless work. This notion is supported by the observations of Grollman,[8] that when an individual moves from sea level to dwell at a high altitude, the cardiac output first increases, but then decreases as polycythemia develops, allowing increased oxygen carrying capacity of the blood to replace increased cardiac output as a means of supplying the tissues with their oxygen requirement.

SUMMARY

1. Measurements of cardiac output by the acetylene method, and of related circulatory functions, have been made on six patients suffering from polycythemia vera, and studies of the blood gases have been made on one of these patients, as well as on another subject suffering from polycythemia vera.

2. At a time when the amount of hemoglobin and the count of the red blood cells were increased above normal, the arteriovenous oxygen difference was increased, the cardiac output per beat and the cardiac index were decreased, and the oxygen content of both the arterial and venous blood was increased. Left ventricular work, cardiac size, basal metabolic rate, blood pressure, and other functions of the circulation studied showed no consistent variation from normal. When reduction of the level of hemoglobin and red blood cells occurred as a result of therapy, the arteriovenous oxygen difference decreased and the cardiac index and output per beat increased and attained normal

*This patient was a white male, aged 42 years, who was observed in the Hospital of the Rockefeller Institute for Medical Research over a period of five months in 1926. He had suffered from symptoms of polycythemia vera for five years and on examination revealed findings typical of this disease, but no other abnormalities. The blood pressure measured 130/100 mm. Hg, and the basal metabolic rate +18.7 per cent. We wish to thank Dr. Alfred E. Cohn of the Hospital of the Rockefeller Institute for Medical Research for permission to use these data.

values when the red blood cells and hemoglobin reached normal levels. There was a linear relationship between quantity of hemoglobin and number of red blood cells on the one hand, and the cardiac output and the cardiac index on the other. These changes in circulation may be compensatory mechanisms which spare the heart part of the burden of pumping an increased total volume of circulating blood having an increased viscosity at a normal velocity.

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Department of Clinical Reports

AN UNUSUAL CASE OF CONGENITAL HEART DISEASE IN A WOMAN WHO LIVED FOR FORTY-FOUR YEARS AND SIX MONTHS

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THE interest of the medical profession in the diagnosis of congenital anomalies has been stimulated in recent years by comprehensive pathologic, physiologic, and clinical observations. Maude Abbott's[1] work in this field has been outstanding, and she has suggested a practical classification. It is briefly as follows:

1. Acyanotic group (no abnormal communication). Examples: coaretation of aorta, bicuspid aortic valve.
2. Cyanose tardive (arterial-venous shunt with temporary or terminal reversal of flow). Examples: Patent ductus arteriosus, patent foramen ovale, interventricular septal defect.
3. Cyanotic group (permanent venous-arterial shunt). Examples: tetralogy of Fallot, Eisenmenger complex.

The vast majority of congenitally diseased hearts are seen by pediatricians, as the more severe and complex lesions are usually fatal in early life. However, lesions falling into the acyanotic group are frequently overlooked or minimized in this period, and likewise, anomalies resulting in arterial-venous shunt are often asymptomatic and may also be overlooked until the stress and strain of advancing years have been added. Consequently, cases in these two groups are those most commonly seen in adults. Rarely do the patients with permanent venous-arterial shunt reach the third decade or beyond. However, our patient, who died in her forty-fifth year, belonged to this third group.

Of the various congenital cardiac anomalies resulting in permanent cyanosis, the tetralogy of Fallot (consisting of pulmonic stenosis, right ventricular hypertrophy, patent interventricular septum, and dextroposition of the aorta) is the most common. The average length of life of eighty-three such patients studied by Maude Abbott[1] was 12.75 years. It was not until 1929 that the maximum life span of 59 years and 9 months was reported by White and Sprague.[2] The mean age of thirty patients with pulmonic atresia with interventricular septal defect and dextroposition of the aorta was 5 years, with a maximum age of 30 years.[3] Seventeen patients with transposition of the arterial trunks with

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interventricular septal defect had a mean age of 2.75 and a maximum age of 16 years.[3] The short duration of life in these cases is noteworthy, and consequently, when a similar group of anomalies is found to exist in an adult, it is of considerable interest.

Our patient, a single, white female, 35 years of age, was first admitted to the Wisconsin General Hospital in November, 1926. Her chief complaint was pain in the upper abdomen. For several years she had experienced intermittent sharp upper abdominal pain associated with nausea. This was not related to food, exercise, or time of day. She had always been dyspneic and cyanotic, and had been told that she had a cardiac murmur from early childhood. Consequently, she had led a rather quiet life, but in general, had been comfortable.

On physical examination there was cyanosis of the lips and nail beds and marked clubbing of the fingers and toes. The chest was somewhat deformed, with a prominent angle of Louis. The heart was enlarged to both right and left. (No definite measurements were recorded.) There was a rough systolic murmur maximum over the pulmonic area; it was widely transmitted over the precordium, but chiefly upward into the left carotid. The second sound at the base was reduplicated. The blood pressure was 150/70; the cardiac rate, 54 to 56; and the rhythm, regular. Hemoglobin was 93 per cent (Tallqvist method), and the erythrocyte count was 5,688,000. An electrocardiogram showed complete heart block (auricular rate 85, and ventricular rate 42), with marked right ventricular preponderance.

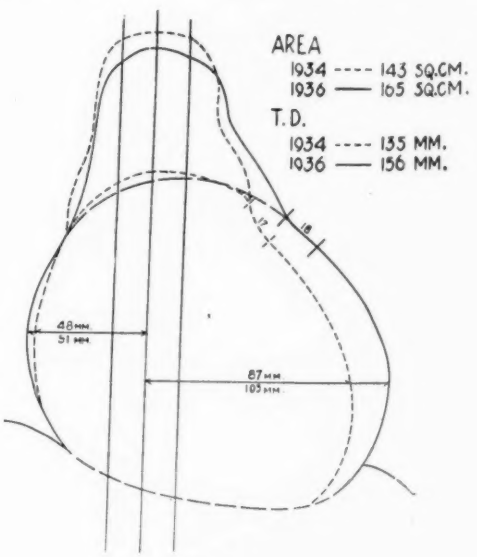

Fig. 1.

She returned on Nov. 13, 1928. The only significant variation in symptoms was an increase in the amount of dyspnea. The degree of cardiac enlargement was believed to be slightly increased. A right ovarian cyst, about 7 cm. in diameter, was now present. Otherwise, the physical findings were essentially unchanged.

Upon examination on Dec. 13, 1934, an orthodiagram was first made. This showed a prominent pulmonic arch, a normal left auricular salient, a narrow retrocardiac space, and marked cardiac enlargement, with a +68 per cent deviation in frontal area and a +21 per cent deviation in transverse diameter. The maximum left diameter was 87 mm., and the right, 48 mm. (Fig. 1).

Her final admission was Sept. 21, 1936. She had continued to be quite active, doing all of the housework for aged parents and herself. On examination it was noted that mentation was sluggish. Dyspnea at rest was present for the first time. Cyanosis had increased. Examination of the circulatory system showed a regular pulse, with a rate of 45. Blood pressure was 125/90 in the right arm and 135/90 in the right leg. The apex impulse was visible and palpable in the fifth interspace 10.5 cm to the left of the midsternal line. There was moderate apical and precordial heaving. The pulmonic second sound was widely split and greater than the aortic second sound. A moderately loud, harsh, systolic murmur was maximum at the pulmonic area, and distinctly heard over the suprasternal notch and in the carotid vessels. A somewhat softer systolic murmur was audible over the sternum at the level of the third and fourth ribs, transmitted to the apex and left axilla. A soft, blowing, early diastolic murmur was best heard along the left sternal border, but was not audible at the aortic area. The liver was palpable 3 cm. below the right costal margin at the midclavicular line. The lungs were clear. There was no peripheral edema. Hemoglobin was 90 per cent (Tallqvist), and the erythrocyte count was 7,400,000. Orthodiascopic examination revealed an increase to +92 per cent deviation in the frontal area and +46.9 per cent deviation in the transverse diameter (Fig. 1). An electrocardiogram showed a persistence of the previous complete heart block, with marked right ventricular preponderance; in addition, T_1 and T_2 were low, T_3 inverted, and T_4 low and diphasic (Fig. 2).

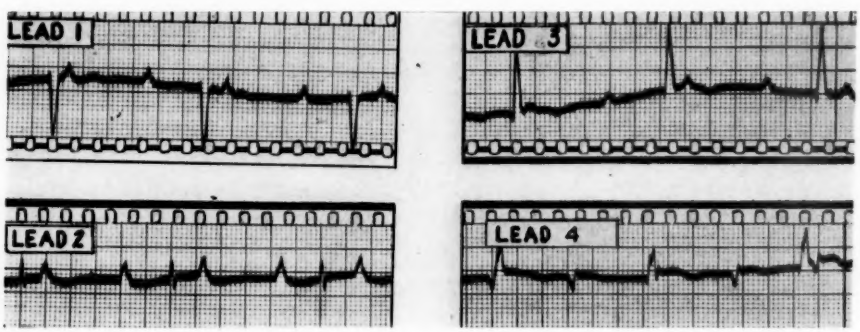

Fig. 2.

During the early portion of this terminal hospitalization, there was little change in the patient's condition, and she was able to be up and about the ward. A dental consultant advised complete extractions, but it was felt that only those teeth which had definite abscesses should be removed. Three days after the extraction of the lower central and lateral incisors she developed swelling and tenderness in the right cervical region. Several days later a similar condition was noted in the right upper extremity. It was believed that she had developed a thrombophlebitis of the right external jugular and right subclavian veins. Her course was rapidly unfavorable from this point, despite the administration of digitalis and oxygen. The venous pressure rose to 20 cm. of water, and 500 c.c. of blood were removed by venesection. Evidence of rapidly progressive decompensation developed, and the patient died two days after the signs of thrombosis of the right subclavian vein were noted. The hemoglobin rose to 100 per cent (Tallqvist), and the erythrocytes to 8,360,000, terminally.

Autopsy Report.—In addition to our general post-mortem examination, the heart was submitted to Dr. Maude E. Abbott, who very kindly examined it. Her report is included in the following.

On external examination, edema of the lower extremities and clubbing of the fingers and toes were found. The right arm and the right side of the neck were swollen and edematous, but no discoloration was noted here. There was cyanosis of the nails and mucous membranes.

Upon opening the pericardium, it was apparent that the position of the heart was abnormal, as the aorta lay anterior to the pulmonary artery. The organ weighed 450 Gm.

DR. ABBOTT'S REPORT ON HEART

External View.—The heart appears to have occupied its normal position in the thorax, but seems to have rotated somewhat on its own axis so that the left auricle lies toward the right posteriorly, entirely at the back of the heart. The ventricular part of the organ is a powerful muscular structure formed in two-thirds of its extent by the right ventricle (as shown by the situation of the interventricular groove), and its apex, which points to the left and is broad and rounded, is formed entirely of the right chamber which curves upward on the left from below around the apex of the left ventricle, producing what may be described as the first degree of "coeur en sabot." The subepicardial fat is increased. The upper left border is very prominent, evidently representing the conus of the right ventricle, and from its extreme upper left angle emerges the transposed aorta in the position normally occupied by the pulmonary artery (Fig. 3). It passes directly upward to form the arch, from which the great vessels are given off in their normal position and relations.

Fig. 3.

Laid open, the aorta is a relatively small trunk, 5 cm. in circumference, just above the aortic valve, and it presents in its arch and thoracic portion some scattered calcified areas and atheromatous patches. Just opposite the origin of the left subclavian artery is a sacculation the size of a bean, in the floor of which are two calcareous plaques, and between these lies the pinpoint orifice of the ductus arteriosus which is a short trunk 1.2 cm. long, with obliterated lumen attached to the left branch of the pulmonary artery where it opens into the bottom of a small tent-shaped diverticulum by a minute opening admitting a bristle.

The pulmonary artery itself emerges transposed from the base of the ventricular portion of the heart on a plane posterior to and to the right of the aorta, which screens it on its left half, while on its right side it is hidden from the anterior view

by the greatly hypertrophied right auricular appendix, which stretches horizontally across it nearly as far as the root of the aorta. It is thin-walled and greatly dilated, with a lumen 8 cm. in circumference at its origin, increasing in size to 10 cm. at its bifurcation. The left auricular appendix is small and is entirely concealed from view anteriorly by the hypertrophied left border of the ventricle.

Interior View.—The right auricle is dilated to approximately three times the capacity of the left and is also hypertrophied, especially in the region of the large auricular appendix where the musculi pectinati are of great size, and its chamber is expanded to the size of a tangerine. The foramen ovale is persistently patent, presenting a slit-like opening 1 cm. long, with thick fleshy borders. The annulus ovalis is present but not well developed. The eustachian and thebesian valves are both absent, and the mouth of the coronary sinus is represented by two small orifices, the lower of which opens into a small venous channel running in the auriculoventricular groove, while the upper leads into a vessel which runs up toward the back of the heart (pervious vein of Marshall?).

Fig. 4.

The tricuspid valve is supplied with three cusps, of which the marginal and infundibular appear normally formed. The "septal" segment, however, is a triangular flap attached at either border to small bundles of papillary muscles derived from the groups on either side, to which the other two cusps are attached, but which has no attachment to the free border of the defective interventricular septum, which lies to its left and posteriorly, presenting a huge defect some 2.5 cm. in diameter, which is screened from the blood entering the sinus of the ventricle from the auricle by the action of this septal cusp. (Fig. 4.)

The sinus of the right ventricle is a roomy chamber with hypertrophied walls, which enters into the formation of the apex and is separated from the left chamber by a muscular septum some 3.5 cm. high in its middle or lowest part, which curves upward at either end to become continuous with the left anterior and right posterior walls of the organ. The free upper border of this septum is a rounded muscular structure with chordae tendineae which are derived only from the mitral valve on the left side of the heart. The defect is bordered on its upper and anterior margin

by the crista supraventricularis of the right ventricle which separates it from the aorta, and on the left posteriorly by a tendinous structure below the transposed pulmonary orifice which apparently represents the aortic vestibule of the left ventricle, the lower border of which gives attachment to the chordae tendineae of the infundibular and septal tricuspid segments.

The upper portion of this right chamber is occupied by a rounded cavity the size of a walnut, demarcated below by a sharp muscular ridge, the right posterior wall of which is formed by the transposed aortic vestibule above mentioned and the base of the hyperplasic pulmonary cusps, and from it emerges the pulmonary artery guarded by two large, thickened cartilaginous and calcified cusps, the left anterior of which presents behind it a low raphe indicating a composite segment (Fig. 5). The sinuses behind these cusps are very deep (1.5 cm.), and take part in the tendinous posterior wall of this chamber.

Fig. 5.

The left auricle is of small size. It presents the crescentic free border of the valvula foraminis ovalis screening the patent foramen ovale and receives the openings of the pulmonary veins. The mitral valve has two normally formed segments, the left anterior of which is attached by its chordae to the free border of the defective ventricular septum and screens this from the lumen of the aorta which arises from the malposed pulmonary conus which has been placed in the growth of the heart on the left side of the ventricular septum, thus "correcting" the transposition that has occurred. There are three aortic cusps of about equal size, one posterior and two anterior, but the left anterior is the "free" cusp, the left coronary artery being given off behind the posterior segment and two right coronary arteries behind the right anterior.

Anatomic Diagnosis.—Transposition of the great trunks, with "correction" of this deformity by a huge defect of the interventricular septum (producing the effect of a cor biatriatum triloculare) and dextroposition of the transposed pulmonary artery, bringing this into the vicinity of the right auriculoventricular orifice, together with malposition of the pulmonary conus which lies contiguous to the mitral orifice and gives off the aorta. Persistent bulbus cordis forming a separate cham-

ber below the transposed pulmonary orifice. Bicuspid and hyperplasic pulmonic valve, with dilatation of the pulmonary artery above this. Hypoplasia and calcification of the aorta. Persistent patency of the foramen ovale. Hypertrophy and dilatation of the right auricle and ventricle, and hypertrophy of the left ventricle. Double right coronary behind right anterior cusp and left coronary behind posterior cusp. Persistent ligamentum arteriosum. (Fig. 6 is a schematic diagram indicating the foregoing mechanism.)

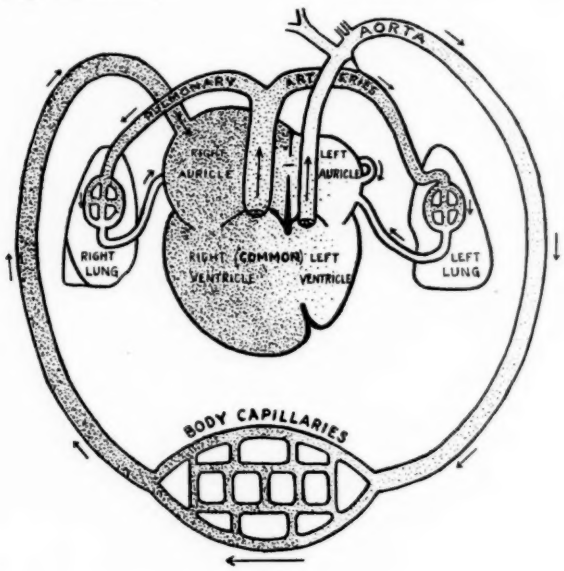

Fig. 6.

Chronic passive congestion of the liver, spleen, and kidneys; edema of the lower extremities; clubbing of the fingers and toes; edema of the right side of the neck and right upper extremity; localized pulmonary atelectasis; uterine polyps; simple cysts of right ovary; fibrous peritoneal adhesions (cause unknown).

Microscopic examination confirmed the gross diagnosis, with the following additional features: Pulmonary emphysema; acute lymphadenitis (bronchial lymph nodes); subacute hepatitis; biliary (obstructive) cirrhosis of the liver; chronic cholecystitis; chronic atrophic gastritis; acute endometritis; cystic changes in endometrium; chronic lymphadenitis (vertebral lymph nodes).

DISCUSSION

Abbott[1] reports six cases of corrected transposition in 1,000 cases of congenital heart disease analyzed. Of these, four are classified as primary lesions and two as complicating other defects. Only one of these persons reached the age of 24 years. She points out that corrected transposition is a rare and still incompletely understood phenomenon. Although Rokitansky's brilliant hypothesis covered eight possible variations, only two of these had been observed by him. In this phenomenon a complete or crossed transposition has occurred, in that the great trunks arise in reversed relations, but the condition is "corrected"[1] from the functional standpoint in that each trunk is placed in its proper ventricle.

In the case reported, the "correction" is accomplished in an unusual way, owing to the fact that the transposition itself is what Rokitansky would call "partial," that is, complicated by a huge defect in the septum. The complete heart block first demonstrated ten years before death is of further interest. It is quite possible that this condition was also congenital, as complete heart block is commonly associated with defects of the interventricular septum.

No record of a patient with this type of congenital heart disease who survived into the forty-fifth year has been found in the literature.

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DISSECTING ANEURYSM OF THE AORTA

Case Report of a Negro With Aortic Regurgitation and Saccular Aneurysm of the Aorta of Nonsyphilitic Origin

Ashton Graybiel, M.D., and Howard B. Sprague, M.D.
Boston, Mass.

UNTIL the past few years dissecting aneurysm of the aorta has not been correctly diagnosed ante mortem save in rare instances.[1-5] There are two chief reasons for this tardy recognition of such a distinct pathologic entity: first, this syndrome has not received sufficient attention until recently; second, a sharply defined clinical pattern is often absent. The very nature of this disorder suggests that it should be accompanied by widely varied clinical manifestations. Thus, a single case often provides an inadequate conception of this syndrome as a whole, but may, as in the present case report, emphasize certain unusual aspects or associations. It is a study of these atypical cases which will advance our knowledge of the disorder.

H. R., a negro male, aged 58 years, was first seen by us in March, 1937, complaining of extreme shortness of breath. For the greater part of his life he had been well and strong despite the excessive strain attending his work as a court stenographer. For a number of years he was known to have had arterial hypertension, and in 1933 he began to complain of headaches, and undue dyspnea on exercise. Examination at that time revealed moderate cardiac enlargement and aortic regurgitation; the blood pressure was 220/90 mm. Hg. Although repeated serologic tests for syphilis were negative, he had been given antisyphilitic therapy over several periods of many months. In June, 1936, he was forced to stop work and since that time had developed increasingly severe headaches, weakness, and dyspnea. Roentgenologic examination in October, 1936, revealed moderate cardiac enlargement and aneurysmal dilatation of the aorta. An electrocardiogram showed marked left axis deviation and inversion of the T waves in Leads I and II.

Our examination revealed a well-preserved, rather thin, alert man, obviously dyspneic. The pupils reacted sluggishly but normally. The heart was greatly enlarged, the sounds were of poor quality, and gallop rhythm was present. At the aortic area a faint systolic murmur was heard, followed by a prolonged high-pitched diastolic murmur. The great vessel percussion dullness was markedly wider than normal. The blood pressure was 240/150. Moist râles were heard over the right lung base, but edema of the shins was not present. A diagnosis was made of hypertensive and probable syphilitic heart disease, with marked cardiac enlargement, slight aortic regurgitation, aneurysm of the aorta, and congestive failure.

Treatment with mercurial diuretics and digitalis resulted in improvement, and the patient passed a comfortable summer. On Sept. 17, 1937, he began to complain of darting pains in the chest. These pains were sharp and fleeting in character and were not related to exercise, excitement, or movement of the thorax. Nausea, shortness of breath, and anxiety were accompanying symptoms. These symptoms abated and examination two days later did not reveal any significant change. Fluoroscopic examination revealed marked cardiac enlargement and dilatation of

From the Cardiac Clinic of the Massachusetts General Hospital.
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the aorta, with saccular expansion in the region of the arch. On September 20 he became nauseated and vomited twice. Cough and fever developed, and the next day he raised a small amount of rusty sputum. Chest pains returned and seemed localized in the left lower thorax. He entered the hospital on the evening of September 21, and examination disclosed signs suggesting consolidation of the lung bases. The blood pressure had fallen to 160/95. He passed a restless night, complaining of pains across the upper chest anteriorly and between the shoulder blades. He died suddenly, early in the morning. An additional diagnosis was made of probable rupture of the aorta, pulmonary embolism, or bronchopneumonia.

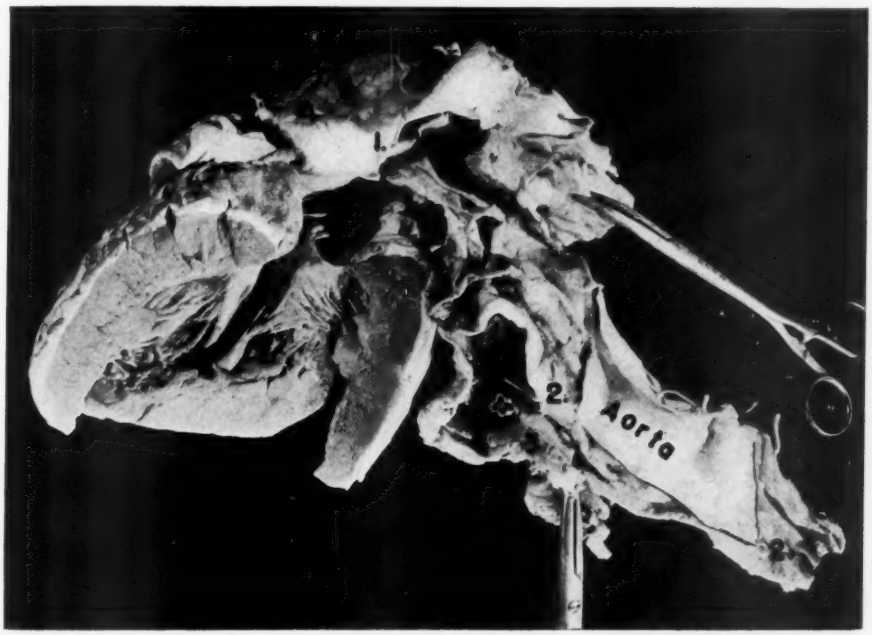

Fig. 1.—Photograph of the heart and aorta. *1*, Original aneurysmal sac resulting from the initial dissection; *2*, second aorta as a result of the original dissection; *3*, sac resulting from the second perforation and showing the final perforation in its center.

At autopsy the left pleural cavity and posterior mediastinum were found to be filled with blood. The left lung was atelectatic save for the anterior half of the upper lobe. The right lung was atelectatic at the base. The heart weighed 600 Gm., the left ventricular wall measuring 25 mm., and the right 8 mm., in thickness. There was very slight thickening of the aortic valve cusps, and the valve opening measured 7 cm. in circumference. The coronary arteries showed only slight atherosclerosis. One of the smaller branches of the left coronary artery contained an old occluding thrombus, but an accompanying area of infarction was not present. The aorta was scarcely recognizable as such. Just proximal to the arch there was a smooth-edged opening through the intima 3 cm. in diameter leading into a large sac 8 by 6 by 4 cm. which extended back to the aortic ring and was partly filled with clotted blood. This sac was adherent to the pericardial surface of the right auricle and a separation between the two could not be made. The wall of the aneurysm was 2 to 4 mm. in thickness and was not only re-epithelialized but showed well-marked atheroma as well. The dissecting aneurysm extended also distally along the arch into the descending aorta and re-entered the left common iliac artery at a point 4 cm. beyond its origin. The dissection was not continued into the

branches of the arch but extended throughout the whole length of each renal artery and into the main branches of the celiac axis. Just above the diaphragm there was a fresh, ragged, oblique tear 1.5 cm. long in the outermost wall of the aneurysm which was the site of a second dissecting aneurysm. Thus, this dissection was in the adventitia of the wall of the original dissecting aneurysm. A third and final tear, at about the same level as the second, produced a rupture into the posterior mediastinal tissues and pleural cavity. Microscopic study of sections from various portions of the aorta did not reveal any evidence of syphilitic aortitis.

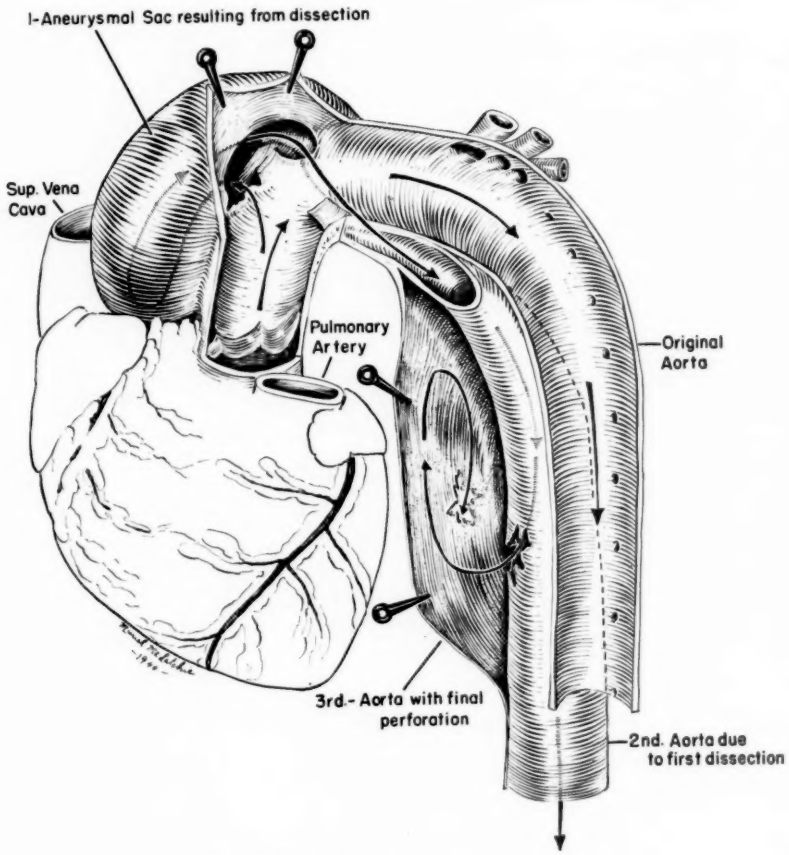

Fig. 2.—Sketch drawn from Fig. 1.

DISCUSSION

Whenever one is confronted with a problem in diagnosis, probabilities play an important role. Thus, given the case of a negro patient with aortic regurgitation, the probability of syphilis as the etiological factor is first considered. If, in addition, there is present a saccular aneurysm of the aorta, the diagnosis of syphilitic aortitis would seem highly probable, if not certain. In the present case these important signs were misleading and had resulted not only in the incorrect diagnosis of syphilitic aortitis but in extended antisyphilitic therapy as well.

Rarely, a dissecting aneurysm has led to the formation of a small saccular aneurysm and rarely aortic regurgitation has been noted as a clinical finding in such cases, but, heretofore, all three in combination have not been described. Only a few cases[1, 3] have been reported in which syphilitic aortitis and dissecting aneurysm coexisted, the pathologic nature of the former being such that it never leads to a dissecting type of lesion.

The original dissection in the present case must have occurred a year or more before death, to judge from the extent of the atheroma in the re-epithelialized portions. However, a history of significant chest pain was not obtained until the final episode. The only symptoms were those of congestive heart failure until shortly before death, when there were sharp fleeting pains in the chest and between the shoulder blades. Even this symptom was confusing because of the lung signs which suggested the possibility of pulmonary infarction. Nevertheless, the fall in blood pressure and the sudden exodus strongly suggested rupture of the aorta. Death might well have occurred at an earlier date due to congestive failure; in that case, the dissecting aneurysm would not have been an important factor in causing death.

This case emphasizes the fact that dissecting aneurysm of the aorta must be kept in mind in all cases of long-standing arterial hypertension. It may exist for years without apparent symptoms, and it may cause death under circumstances which make diagnosis difficult.

SUMMARY

A case is reported of a negro male, 58 years of age, with prolonged hypertension and dissecting aneurysm which occurred without any known history of severe chest pain. No evidence of syphilis was found at autopsy, and the Hinton reaction was negative. The original dissection had resulted in a rupture back into the lumen of the aorta, so that a double-barreled aorta was formed. This second aorta must have been present for a long time because there were atheromatous changes in the re-epithelialized surface. Death was due to a rupture and dissection into the adventitial space of the second aorta which, in turn, ruptured into the mediastinal space and pleural cavity.

Another case, having somewhat similar pathologic features (dissecting aneurysm of long duration, with sclerosis of the new aorta) and correctly diagnosed ante mortem, has been observed by Dr. Paul D. White.

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Department of Reviews and Abstracts

Selected Abstracts

Smith, Lucian A., Allen, Edgar V., and Craig, Winchell McK.: Time Required for Blood to Flow From the Arm and From the Foot of Man to the Carotid Sinuses: I. Effect of Temperature, Exercise, Increased Intramuscular Tension, Elevation of Limbs, and Sympathectomy. Arch. Surg. 41: 1366, 1940.

The mean circulation time from the arm to the carotid sinus of normal persons in the present study was 20.1 seconds. The range was 12.4 to 33.2 seconds. The mean circulation time from the foot to the carotid sinus was 38.7 seconds. The range was from 22 to 67 seconds.

The temperature of the skin of the extremities and the circulation times from foot to carotid sinus and from arm to carotid sinus are closely related. Warmth of the skin decreases the circulation time, and coldness of the skin increases it.

Exercise of the legs, elevation of an extremity, lumbar sympathectomy, and increase of intramuscular tension caused by strychnine decrease circulation time in the part concerned.

NAIDE.

Smith, Lucian A., and Allen, Edgar V.: Circulation Time From Foot to Carotid Sinus and From Arm to Carotid Sinus of Man: II. Effects of Operation and of Administration of Thyroid Gland; Post-Operative Phlebitis and Pulmonary Embolism. Arch. Surg. 41: 1377, 1940.

Following a variety of surgical operations carried out under different anesthetic agents, it was found that the foot to carotid sinus circulation time is usually increased after the fourth day, that is, blood flows more slowly. Increases in the circulation time from the arm to the carotid sinus are less common and less marked. The slowing of venous circulation is probably an important factor in the complicated mechanism of postoperative venous thrombosis and pulmonary embolism.

Administration of thyroid gland to normal subjects decreases circulation time, that is, increases the rate of flow of blood from the arm and from the foot to the carotid sinus. Postoperative administration tends to prevent the slowing of venous circulation which commonly occurs after operation.

NAIDE.

Guttmann, E., and Jones, Maxwell: Hyperventilation and the Effort Syndrome. Brit. M. J. 2: 736, 1940.

Fifty-two cases of effort syndrome have been hyperventilated. In only 50 per cent of them were clinical symptoms reproduced in this way, and in these the symptoms were those which one commonly associates with tetany, e.g., paresthesia and disturbances of consciousness, rather than those characteristic of effort syndrome. We feel that, in view of our findings, we cannot support the contention of some workers that hyperventilation has an important place in the etiology of effort syndrome.

AUTHORS

Spillane, John D.: Observations on Effort. Syndrome. Brit. M. J. 2: 739, 1940.

The group of patients who are diagnosed as suffering from the effort syndrome are psychoneurotics in whom somatic manifestations, in the cardiovascular sphere, are prominent. Psychologic difficulties are also present, but are frequently masked. There is no evidence that a fundamental physiologic defect is at work in the majority.

AUTHOR.

Bredt, H., and Stadler, L.: The Appearance of the Lesser Circuit in Inflammatory Heart Failure and Its Significance in the Clinical Picture. Arch. f. Kreislaufforsch. 7: 54, 1940.

Thirty-seven cases of rheumatic heart disease with valvular involvement were the basis of the study. Pulmonary vessels were examined microscopically. Involvement was noted in the arteries, arterioles, and veins and consisted of inflammatory reactions, proliferation of intima, encroachment of the lumina, and disappearance of media. These changes are attributed to the same processes as those causing the endocarditis. These pulmonary endarteritides are thought to contribute to the clinical picture, especially the cyanosis and dyspnea.

KATZ.

Morelli, Alberto C.: Extra Rapid Tomography in the Examination of the Circulatory Apparatus. Rev. argent. de cardiol. 7: 217, 1940.

A modification of the method of Vallebona and Bozetti is described for extrarapid tomography applicable to the radiologic study of the heart, pulmonary vessels, and mediastinum.

The modifications consist in the employment of very deep rays in reduced areas and in the kind of movement which the patient undergoes.

During the first half of the run the movement is progressively accelerated, and during the second half it is symmetrically retarded. The x-ray picture is obtained during the end of the first and the beginning of the second half period.

With this system, since the angular velocity is greater at the center of the angle in which the picture is obtained, the amount of x-rays which the body receives at the lateral limits of the angle will be greater, the dispersion effect in those planes out of focus will also be greater, and, therefore, the tomographic effect will be better the smaller the angles of displacement.

These extrarapid tomographies (exposures of 0.03 to 0.1 second) are clearer (a) the smaller the angle of the run, (b) the shorter the time of exposure, (c) the greater the difference in velocity between beginning and end of the rotation movement (when the velocity is smaller) and the center of the run where the velocity is greater, and (d) the greater the penetration of the x-rays. There are other minor factors, such as focus of the x-ray tube, distances, tube-film, and patient-film, mechanical vibrations, etc., which may be important.

AUTHOR.

Peet, Max Minor, Ward, Wilson Woods, and Braden, Spencer: The Surgical Treatment of Hypertension. J. A. M. A. 115: 1875, 1940.

Three hundred and fifty consecutive cases of hypertension with operation by bilateral supradiaphragmatic splanchnicotomy and lower dorsal sympathetic ganglionectomy have been studied over a period of nearly seven years.

Of the patients studied, 86.6 per cent had postoperative relief of major symptoms, especially headache, 81.3 per cent had improvement or complete relief of incapacita-

tion, and 51.4 per cent with adequate postoperative data had a significant reduction in blood pressure. In approximately one-half of these patients pressures fell to normal or were markedly reduced.

Improvement in ophthalmologic, cardiac, and renal status following operation occurred in from 45 per cent to 70 per cent of the cases studied.

Prognosis was much more favorable in females than in males.

The most favorable results were obtained in the age group before 30. Following this period age appeared to be of minor importance.

Far-advanced fundus changes, i.e., marked angiospasm and papilledema, were not contraindications to the operation.

The operative mortality was low (3.4 per cent), and no specific ill effects were attendant on the operation.

Finally, no other form of therapy, whether medical or surgical, which offers such good results in patients suffering from hypertension of an equal degree of severity has, as yet, been reported. Furthermore, these results are not temporary but continue over a period of years.

The conclusion is reached that the surgical treatment of hypertension by bilateral supradiaphragmatic splanchnicotomy and lower dorsal sympathetic ganglionectomy offers a better prognosis in cases of severe hypertension than any other form of therapy as yet reported.

NAIDE.

DeTakats, Geza, and Scupham, George W.: Revascularization of the Ischemic Kidney. Arch. Surg. **41**: 1394, 1940.

Four hypertensive patients in whose cases the diagnosis of malignant nephrosclerosis was made were operated on with the idea that the ischemic kidney might obtain some additional circulation. The kidneys were decapsulated; the cortex was incised; and the omentum or a pedicled muscle flap was wrapped around the kidney. The four case reports are summarized. One patient has been followed for three and one-half years. In no patient was there a definite improvement. It is possible that, if patients with essential hypertension with earlier or more proximal vascular damage were subjected to such a procedure, the condition might be arrested or improved. The importance of taking renal biopsy specimens and the difficult interpretation of biopsy observations in the early stages are emphasized. For the late stages in which the patient is referred to the surgeon, renal vascularization has been of no value.

NAIDE.

Moss, H. K., and Herrmann, L. G.: Use of Quinine for Relief of "Night Cramps" in the Extremities. J. A. M. A. **115**: 1358, 1940.

Fifteen patients who suffered from "night cramps" were treated successfully with quinine sulfate. It is thought that quinine acts on the myoneural junction and may be the antagonist of prostigmine.

SCHWARTZ.

Fetter, Ferdinand, and Schnabel, Truman G.: The Behavior of the Blood Sedimentation Rate During and After Fever Therapy. Am. J. M. Sc. **201**: 115, 1941.

Sedimentation rates were determined on forty-one patients who were receiving physically induced fever in the hypertherm. Determinations were made before, during, immediately after, and the day after the fever treatment.

No significant variations in the sedimentation rates were found in these four determinations.

For practical purposes, physically induced fever used therapeutically does not affect the sedimentation rate.

An accurate determination of the sedimentation rate can, therefore, be made at any time during or after a fever session.

AUTHORS.

Gammon, George D., and Starr, Isaac, Jr.: Studies on the Relief of Pain by Counterirritation. J. Clin. Investigation **20**: 13, 1941.

After inducing pain on themselves by the subcutaneous injection of 10 per cent NaCl or the application of irritant ointments, the authors studied the relief brought by counterirritation of various types, e.g., heat, cold, the electric current, vibration, and tactile stimulation.

Irrespective of the type of pain and counterirritant, a definite pattern usually appeared; the application of counterirritation caused temporary relief; its removal was also followed by temporary relief.

Experiments demonstrated that the relief secured was not due to changes in the circulation. Animal experiments in which the discharge from sensory nerves was recorded yielded results which are analogous to some of the changes of sensation experienced. On the other hand, other changes of sensation could not be accounted for by an altered sensory discharge. We have discussed the possibility that they are due to a central depression of the pain.

As periodic counterirritation produced the maximum of relief of pain induced in the authors themselves, apparatus was devised for the intermittent application of heat and cold to patients.

While there is great difficulty in judging the effectiveness of agents acting on the sensation of patients, we have gained the impression that by wise selection and periodic application of counterirritants much more relief can be secured than by the haphazard application of hot water bottles and ice bags which was our former practice.

AUTHORS.

Castleden, L. I. M.: The Effect of Potassium Salts on Cardiac Irregularities. Brit. M. J. **1**: 7, 1941.

The administration of potassium salts caused the disappearance of extrasystoles in one case in which they were associated with insulin hypoglycemia and in four in which they were spontaneous.

In three of these five cases the level of potassium in the serum was estimated, and the disappearance of the extrasystoles was associated with a rise in potassium level.

Attempts to produce extrasystoles by the administration of ephedrine were not successful. In contrast with insulin and adrenaline, ephedrine does not produce consistently a fall in the serum potassium.

Potassium salts have been reported to produce cardiac irregularities in experimental animals and to increase the incidence of extrasystoles and paroxysmal tachycardia in some patients, so that their action in suppressing extrasystoles cannot be utilized with confidence in the treatment of patients until further work has clarified the mechanism of these effects.

AUTHOR.

Glyn-Hughes, F., and Spence, A. M.: Sulphonamide Therapy in Lupus Erythematosus. Brit. M. J. 2: 741, 1940.

There was a definite response to sulfonamide therapy in each of the twelve cases cited, a point which strongly supports the theory of a streptococcal origin of the disease. In fact, even among the failures some of the chronic sufferers were very loath to abandon the treatment because of the hopes to which the initial success had given rise. Six patients, or 50 per cent, were completely healed and have remained so. The existence of some latent and resistant focus of infection is the probable cause of failure in the other cases. One patient relapsed twice, but, after a previously overlooked cervical erosion had been treated, she was completely cured.

The successful cases included all those patients who had not suffered from the disease for more than a year. When it is considered that roughly 25 Gm. of sulfonamide administered over a period of about four weeks has been successful in clearing up what is regarded as an intractable disease, the effect of the drug appears well-nigh specific and suggests that the prognosis in early cases is very favorable.

AUTHORS.

Wolff, H. G., Hardy, J. D., and Goodell, H.: Measurement of the Effect on the Pain Threshold of Acetylsalicylic Acid, Acetanilid, Acetophenetidin, Aminopyrine, Ethyl Alcohol, Trichlorethylene, a Barbiturate, Quinine, Ergotamine Tartrate, and Caffeine: An Analysis of Their Relation to the Pain Experience. J. Clin. Investigation 20: 63, 1941.

Quantitative measurements of the pain threshold were made by irradiating 3.5 sq. cm. of skin surface for three seconds. The intensity of radiation which barely evoked pain was denoted as the pain threshold. The threshold-raising action of various nonopiate analgesic agents was then ascertained in terms of the normal threshold.

Acetylsalicylic acid (oral) in quantities of 0.03 Gm. to 1.8 Gm. was thus assayed. The minimum effective quantity of this agent is 0.06 Gm. (0.9 mg. per kilogram of body weight). The "saturation" quantity or the smallest amount with which the highest threshold-raising effect was attained was 0.3 Gm. The highest threshold-raising effect of which the agent was capable was approximately 35 per cent above the control threshold, and the maximum threshold-raising effect for quantities of acetylsalicylic acid, in amounts of 0.06 Gm. to 1.8 Gm., was attained in approximately 50 to 100 minutes.

The time-action curves of threshold-raising effect for acetylsalicylic acid revealed that essential elimination increased at a constant rate with quantities up to 0.3 Gm. However, with larger quantities of the agent, there was acceleration of the essential elimination rate so that durations of effect with 0.9 Gm. and 1.8 Gm. differed but slightly.

The pain threshold-raising action of 0.3 Gm., respectively, of acetanilid, acetophenetidin, and aminopyrine were measured. In these amounts these agents had time-action curves similar to that obtained with 0.3 Gm. of acetylsalicylic acid.

Acetylsalicylic acid induced mild relaxation and lethargy. Acetanilid and acetophenetidin in comparable amounts induced greater relaxation and lethargy and difficulties in mentation. The therapeutic effectiveness of the latter agents rests in good part on their effects.

The pain threshold-raising actions of 30 c.c. and 60 c.c. of ethyl alcohol (oral) were measured. In these amounts the alcohol had a maximum threshold-raising action of 40 per cent above the control level. The larger amount had a longer duration but no greater threshold-raising action.

The pain threshold-raising action, as well as other observable effects, of acetylsalicylic acid, acetanilid, acetophenetidin, and ethyl alcohol was relatively slightly reduced by pain. A uniform pain stimulus was introduced just before or during the first sixty minutes after administration of the agents. Thus, the antagonism between pain and threshold-raising action noted in the case of the opiates is less evident or absent in the case of the above-mentioned agents.

Some effects of alcohol were akin to those of the opiates. Of special significance in both were the emotional states referred to as freedom from anxiety and feelings of contentment and detachment. While in these states, the subjects perceived pain, but they were indifferent to it. Thus like the opiates but perhaps to a lesser degree, alcohol accentuates the ability to dissociate pain perception from the pattern of reaction to pain.

The pain threshold-raising action of 1 c.c. of trichlorethylene (inhaled) was measured. It had a maximum threshold-raising action of approximately 40 per cent above the control level.

The pain threshold-raising action of 0.5 Gm. of the sodium salt of N-methylcyclohexenylmethyl barbituric acid (''Evipal'' brand) was measured. It had a maximum threshold-raising action of approximately 20 per cent above the control level and induced profund lethargy and defects in mentation.

Caffeine sodiobenzoate, ergotamine tartrate, and quinine sulfate had no pain threshold-raising properties.

Various combinations of acetylsalicylic acid, codeine, acetanilid, acetophenetidin, the barbiturates, and caffeine were studied. The pain threshold-raising effect of any combination was no greater than that of its most effective ingredient. Sedative and hypnotic effects, as well as defects in motility, seemed to be summative. A combination of these agents is therapeutically valid if it aims to attain useful psychologic effects coupled with pain threshold-raising action. It is not valid, however, if it be assumed that the pain threshold-raising effects of the different ingredients will summate.

AUTHORS.

Davis, Loyal, and Barker, M. Herbert: The Depressor Effect of Potassium Sulfocyanate Before and After Bilateral Splanchnicotomy in Normal and Hypertensive Dogs. J. Lab. & Clin. Med. **26**: 658, 1941.

From the results of acute experiments carried out upon normal dogs, ischemic hypertensive dogs, and normal dogs with elevated blood cyanate levels, it would seem logical to believe that the effect of the intravenous injection of potassium sulfocyanate produces its depressor effect as the result of a general vasodilatation. This effect can be increased by removal of the thoracic sympathetic trunk and splanchnic nerves supradiaphragmatically. These experimental observations lend support to the observation made clinically that in many instances patients who respond poorly to cyanate therapy may become sensitive following a bilateral splanchnicotomy.

AUTHORS.

Page, Irvine H., Helmer, O. M., Kohlstaedt, K. G., Fouts, P. J., and Kempf, G. F.: Reduction of Arterial Blood Pressure of Hypertensive Patients and Animals With Extracts of Kidneys. J. Exper. Med. **73**: 7, 1941.

Extracts of kidneys containing a substance which lowers arterial blood pressure for prolonged periods in patients with essential and malignant hypertension and in hypertensive dogs and rats have been prepared.

Several different chemical procedures are proposed for the preparation of the extract. The best one has not been determined.

The quantity of original fresh whole kidney required to yield enough extract to lower blood pressure from hypertensive levels (200 mm. Hg mean pressure) to normal levels is roughly 600 to 900 Gm. in dogs within four to eight days. In hypertensive patients the yield of 700 to 1,000 Gm. daily for several weeks may be necessary.

Lowering of the blood pressure too rapidly in animals results in a shock syndrome which may be fatal. If overdosage is avoided, no appreciable rise in blood urea nitrogen occurs, nor do other signs of toxicity appear.

Lowering of blood pressure to nearly normal levels has been accomplished in sixty hypertensive dogs, and in some of these the blood pressure was allowed to rise and was again reduced as many as five times. Similar results have been obtained with hypertensive rats.

The effect of treatment on six patients with essential hypertension was prolonged reduction of blood pressure. Clinically the patients appeared improved.

Five patients with malignant hypertension have been treated, with reduction of the blood pressure in all instances. One patient was treated despite urea clearance of 5 per cent of normal. His blood pressure was sharply reduced, but death caused by uremia occurred. The second patient also exhibited sharp reduction of pressure and diet after treatment was discontinued. The other three were much improved after treatment, as indicated by increase in vision and mental activity, loss of dyspnea, improvement in the electrocardiogram, etc.

The length of time the blood pressure remains lowered varies greatly in both animals and man. The trend is usually upwards after treatment has been discontinued for four to six days.

Increasing experience with this treatment suggests that it is of value in the management of hypertension, but it is still in the experimental stage.

AUTHORS.

Wang, S. C., and Ranson, S. W.: The Role of the Hypothalamus and Preoptic Region in the Regulation of Heart Rate. Am. J. Physiol. **132**: 5, 1941.

The typical rise and afterfall in the plasma potassium concentration following epinephrine injection have been confirmed in the dog and have been found to be present in sheep and goats.

The active uptake of potassium by the muscles in this connection has been confirmed in dogs.

In the hind limbs of the frog perfused with gum acacia-Ringer the uptake of potassium from the perfusion fluid has been found to be independent of the rate of flow. Epinephrine has not been found to have a direct effect.

The hind limbs of the frog similarly perfused and indirectly stimulated nine times per minute have been found to lose potassium at the rate of 0.5 to 0. gamma of potassium per gram of hind limb per minute.

If a constant perfusion of epinephrine is used with the stimulated mu 'es, it has been found to reduce the rate of potassium loss by 40 per cent.

AUTHORS.

Mendlowitz, Milton: Measurements of Blood Flow and Blood Pressure in Clubbed Fingers. J. Clin. Investigation **20**: 113, 1941.

The Stewart method for measuring blood flow has been shown to be accurate when applied to the finger tip.

The normal range of variation of blood flow and brachial-digital pressure gradient, after release of sympathetic tone, has been determined.

In essential hypertension, aplastic anemia, hyperthyroidism, acromegaly, and diverse chronic infections, all without clubbing, the blood flows and pressure gradients were within the normal range.

In all the varieties of simple clubbing studied, except hereditary clubbing, the blood flows per unit surface or volume of finger tip were abnormally high. These excessive flows were caused, in part at least, by elevated digital arterial pressures. Since the brachial-arterial pressures were unchanged, the brachial-digital gradients were reduced. After incision and drainage of a lung abscess, the previously increased blood flow and digital-arterial pressure returned to normal with recession of the clubbing. It is therefore apparent that abnormally high blood flow and digital-arterial pressure after release of sympathetic tone are peculiar to ordinary clubbing and integral forces in its development. In hereditary clubbing the normal blood flow per unit of tissue and the normal pressure values found indicate that the mechanism of clubbing here is different from that which operates in the ordinary cases.

In hypertrophic osteoarthropathy the blood flow per unit of tissue and the digital-arterial pressure were within normal limits. Since the mean digital-arterial pressure can never be higher than the mean brachial, the increase in digital-arterial pressure, and hence in digital blood flow in simple clubbing without bone changes, is limited. As the circulatory derangement associated with clubbing advances, therefore, it is possible that there is a recession or at least a stabilization of the phenomenon in the finger tips and that the process of increased blood flow and hypertrophy is taken over by the bones.

AUTHOR.

Castex, Mariano R., Battro, Antonio, and González S, Robert: Diagnosis of the Site of Origin of Ventricular Extrasystoles in Human Beings. Arch. Int. Med. **67**: 76, 1941.

Electrocardiograms and phonocardiograms registered simultaneously with tracings of central arterial or venous pulse allow us to prove asynchronism of ventricular contraction and also to determine which of the ventricles contracts first.

In this manner we have studied twenty-three cases of spontaneous extrasystoles in human beings (ten showing negative deflection and thirteen, positive deflection in Lead I), and we have been able to determine to which ventricle corresponds the priority in contraction.

When extrasystole occurs with a negative deflection in Lead I, the data obtained show that the left ventricle contracts before the right one.

When extrasystole occurs with a positive deflection in Lead I, the manifestations of asynchronism show priority of contraction in the right ventricle over that in the left one.

Because of the facts stated, we consider ourselves justified in concluding that premature beats with negative deflections in Lead I originate in the left ventricle and those with positive deflections in Lead I, in the right ventricle.

AUTHORS.

Friedman, Meyer, Selzer, Arthur, and Rosenblum, Harold: The Renal Blood Flow in Coarctation of the Aorta. J. Clin. Investigation **20**: 107, 1941.

The effective renal blood flow and the rate of glomerular filtration were measured by means of the diodrast and inulin clearances, respectively, in a group of eleven normal control subjects and in a group of six patients with coarctation of the aorta.

The findings in the cases of coaretation indicated an appreciable decrease in renal blood flow as compared to the normal subjects. The glomerular filtration rate, however, was normal.

The arterial hypertension in coaretation is interpreted in the light of primary reduced renal blood flow associated with secondary glomerular efferent arteriolar spasm. A probable relationship of these factors to the pathogenesis of essential hypertension is pointed out.

AUTHORS.

Garvin, Curtis F.: Mural Thrombi in the Heart as a Source of Emboli. Am. J. M. Sc. **201:** 412, 1941.

In 771 consecutive adult autopsied patients who died of heart disease, pulmonary infarction was almost three times as frequent in those cases with mural thrombi in the right side of the heart as in those cases without. Infarcts of the brain, kidneys, spleen, intestines, and/or extremities were more than twice as common in cases with mural thrombi in the left side of the heart as in their absence. A similar relationship was found to exist in regard to hypertensive heart disease, coronary artery disease with or without myocardial infarction, and rheumatic heart disease, with one exception. In coronary artery disease without myocardial infarction, infarcts in the brain, kidneys, spleen, intestines, and/or extremities were 1.7 as frequent when mural thrombi were present in the left side of the heart as in their absence, but the difference was not statistically significant. This exception may be due to the small size of the series and/or to the fact that these cases showed considerable peripheral vascular disease which no doubt increased the incidence of infarction due to thrombosis in situ. These observations indicate that mural thrombi in the heart are a significant cause of embolic occlusion of arteries in both the lesser and greater circulations.

AUTHOR.

Hutcheson, William C.: An Anatomic Basis for Auricular Fibrillation. Arch. Path. **31:** 369, 1941.

It is believed that auricular fibrillation in patients with chronic rheumatic heart disease may be due to substitution of auricular smooth muscle for striated cardiac muscle.

AUTHOR.

Baggenstoss, Archie H., and Rosenberg, Edward F.: Cardiac Lesions Associated With Chronic Infectious Arthritis. Arch. Int. Med. **67:** 241, 1941.

In a study at necropsy of twenty-five cases of chronic infectious (rheumatoid) arthritis, cardiac lesions were demonstrated in twenty. Lesions identical with those of rheumatic fever were observed in fourteen (56 per cent). Nonrheumatic cardiac lesions were present in six (24 per cent). In ten of the fourteen cases in which there were rheumatic lesions there was histologic evidence that the inflammatory process was still active and progressive at the time death occurred. In seven of the fourteen instances associated with rheumatic cardiac lesions, the heart disease was judged to be an important factor in causing death. In only seven of the fourteen instances associated with rheumatic cardiac lesions had signs or symptoms of heart disease been present during life. The high incidence of rheumatic cardiac lesions in this series is suggestive of a relationship between chronic infectious (rheumatoid) arthritis and rheumatic fever.

AUTHORS.

Kahn, Joseph R., and Ingraham, Edgar S., Jr.: Cardiac Hypertrophy and Coronary Arteriosclerosis in Hypertension. Arch. Path. **31**: 373, 1941.

Within the limitations of this sort of statistical study, the results suggest that arteriosclerosis of the coronary arteries may play a part in the genesis of cardiac hypertrophy in patients with prolonged hypertension.

AUTHORS.

Katzenstein, Rolf, and Murphy, James Peter: Acute Sclerosing Vascular Disease With Renal Changes. Arch. Int. Med. **67**: 579, 1941.

An unusual case of vascular disease, occurring in a 22-year-old woman, is presented. Sclerosing changes in small arteries, without thrombosis, characterized the vascular lesions. The cause of the condition is entirely unknown. Clinically, the illness simulated bilateral renal cortical necrosis. Arteriolar lesions (with subsequent cerebral injury) were noted, and their possible pathogenesis is discussed.

AUTHORS.

Burrett, John B., and Scherf, David: The Clinical Importance of Small Intracutaneous Veins in the Human Chest. Am. J. M. Sc. **201**: 399, 1941.

Ectasia of small intracutaneous veins located in the neighborhood of the pleural sinuses is described. An examination of 385 patients revealed that the appearance of these veins is not the result of pulmonary, pleural, or cardiac disease. They are found in healthy people. Their incidence increases with age. An explanation of their developmental mechanism is offered.

AUTHORS.

Steinbrocker, Otto, and Samuels, Saul S.: The Arterial Circulation of the Lower Extremities in Chronic Arthritis. J. Lab. & Clin. Med. **26**: 974, 1941.

In a clinical investigation of rheumatoid arthritis, 65.9 per cent of the patients showed abnormalities, usually vasomotor disturbances, of the arterial circulation of the lower extremities; in osteoarthritis 35.2 per cent of the cases presented similar findings. Three rheumatoid patients, or 6.3 per cent had simultaneous arteriosclerotic occlusive disease; two with osteoarthritis, or 2.8 per cent, presented evidence of arteriosclerosis obliterans.

Study of those patients with arthritis presenting arterial abnormalities showed no direct, consistent relationship between the location of the vascular signs and the site of the arthritic process. The evidence suggests that the vasomotor disturbances in chronic rheumatoid arthritis and related conditions may be attributed to some systemic reaction probably acting through the sympathetic nervous system, although in some cases a local irritative reflex vasospastic mechanism in the painful arthritic extremity cannot be ruled out.

In a control group of eighty-six patients with advanced organic arterial disease twenty-eight, or 32 per cent, offered a history, physical signs, or roentgen changes of rheumatic or arthritic involvement at some time. These findings approximate the incidence of such ailments in similar age groups of persons without arterial disturbances and contribute clinical evidence that pronounced arterial disease alone does not usually produce arthritic signs and symptoms.

AUTHORS.

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